

Delirium as a marker of undiagnosed dementia in  
the general hospital: Evaluation of pragmatic  
methods of screening and follow-up

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# Abstract

Delirium is an acute neuropsychiatric syndrome commonly affecting older people in general hospital. Dementia is common in older people in hospital with a distinct phenotype. Delirium and dementia commonly co-exist and are associated with adverse outcomes. The aims of the thesis were to develop pragmatic methods to screen for dementia in patients with delirium and to examine the outcomes of people with delirium. A prospective cohort study of older people admitted to hospital with delirium was carried out.

Cognitive impairment was common among older people with delirium, with 3 in five having dementia and 1 in 5 having unrecognized dementia. Previously published dementia screening tools are scarce and not valid in people with delirium. Informant tools (the IQCODE and AD8) are highly sensitive and specific to detect dementia and combined cognitive impairment (MCI or dementia) in delirium. Delirium duration, severity, the hypoactive subtype and dysregulated inflammation were predictors of adverse outcomes in older people with delirium.

This thesis confirms the close relationship between delirium and dementia in general hospitals. It offers pragmatic solutions to both screening for dementia in older people with delirium, and improving follow-up by detailing predictions of adverse outcome.

*For Clare, Lauren and Alexander*

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To the black dog, whose constant companionship in varying degrees, has triggered a determination to achieve the very best possible.

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# Publications

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Griffiths, S. E., Tandon, U., Treml, J. & Jackson, T. 2014. Delirium in trauma. *Trauma*, 16, 87-92.

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# Conference Proceedings

## Conference presentations arising directly from this thesis

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Jackson T. A., MacLullich A. M., Gladman J. R., Lord J. M., Sheehan B. Undiagnosed long-term cognitive impairment in acutely hospitalised older medical patients with delirium: a prospective cohort study. European Delirium Association Scientific Meeting, London, September 2015 (Poster)

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# Abbreviations

ACEIII	Addenbrooke's Cognitive Examination III
AD8	AD8: The Washington University Dementia Screening Test
AMTS	Abbreviated Mental Test Score
APACHE II	Acute Physiology and Chronic Health Evaluation II
BBB	Blood brain barrier
CAM	Confusion Assessment Method
CDU	Clinical decisions unit
CNS	Central nervous system
CRP	C reactive protein
CSF	Cerebrospinal fluid
DHEA	Dehydroepiandrosterone
DHEAS	Dehydroepiandrosterone sulphate
DRS-R-98	Delirium Rating Scale Revised Version
DSB	Digit span backwards
DSD	Delirium superimposed on dementia
DSF	Digit span forward
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM 5	Diagnostic and Statistical Manual of Mental Disorders fifth edition
DSM-III	Diagnostic and Statistical Manual of Mental Disorders third edition

DSM-IV	Diagnostic and Statistical Manual of Mental Disorders fourth edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders fourth edition text revision
ELISA	Enzyme-linked immunosorbent assay
HPA	Hypothalamic-pituitary-adrenal axis
ICD-10	International Classification of Disease, edition 10
ICU	Intensive care unit
IL-	Interleukin
IQCODE	Informant Questionnaire of Cognitive Decline in the Elderly
LPS	Lipopolysaccharide
MCI	Mild cognitive impairment
MDAS	Memorial Delirium Assessment Scale
MOOSE	Meta-analysis of observational studies in epidemiology
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
STROBE	Strengthening the reporting of observational studies in epidemiology
TNF	Tumour necrosis factor
#	Bone fracture



# 1 Introduction

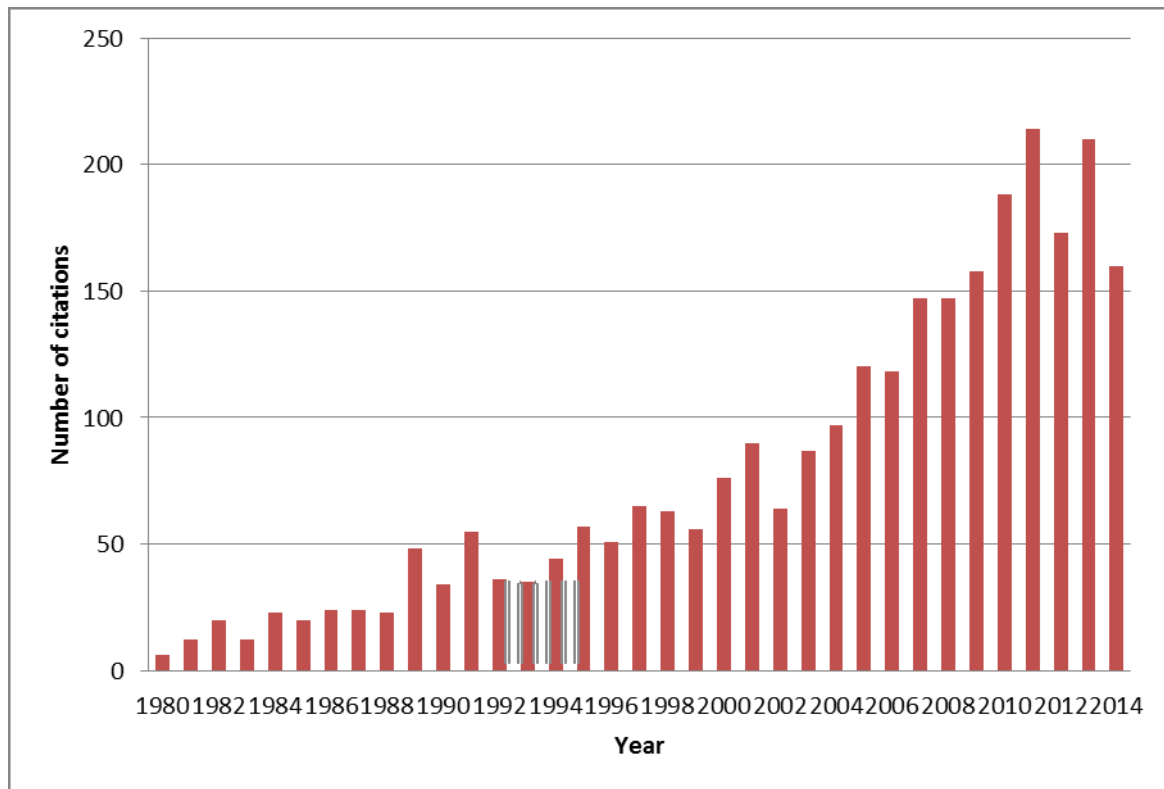
As the population ages there is an increased need for hospitals to understand and manage age related conditions and to try and tailor services to specific age-related health problems (Oliver, 2014). Age-related syndromes such as frailty are associated with a number of specific conditions, often described as the Geriatric Giants, first described in 1965 (Isaacs, 1965). ‘Intellectual failure’ was one of these four original ‘giants’ encompassing both delirium and dementia (Isaacs, 1992). Both delirium and dementia are disorders of cognitive function and are associated with adverse health outcomes. Both conditions are common in general hospitals (Siddiqi et al., 2006, Mukadam and Sampson, 2011) with 20% of older people presenting to hospital having delirium, and 40% of older hospital admissions having dementia. Therefore it is clear that a better understanding of how to assess manage, and follow up these conditions is vital to improving general hospital care to older people (Russ et al., 2012).

This introductory chapter will firstly describe delirium in detail: why older people develop delirium; how to define delirium; how delirium presents to hospital; the importance of delirium in terms of epidemiology; the predictors of adverse outcomes in delirium; and the current understanding of the pathophysiology of delirium. Secondly, the chapter will describe dementia and in particular the typical presentations of dementia seen in general hospitals. Finally, the chapter will explore the relationship between delirium and dementia, in particularly looking at whether delirium is merely a herald of pre-existing dementia or is a cause of dementia itself. Following this the hypothesis and aims of the thesis will be stated.

## 1.1 Delirium

Delirium is a serious acute neuropsychiatric condition affecting mainly older people in hospitals. It is a disorder of global cognitive function, typically attention and working memory, as well as consciousness (Fong et al., 2009b, Inouye et al., 2014, MacLulich et al., 2013). Delirium often goes unrecognised, yet affects between 14 and 24% of acute hospital admissions, developing as a new disorder during 6 to 56% of inpatient stays (Inouye et al., 2014). The clinical presentation of patients with delirium is varied and two specific motor sub-types, hyperactive and hypoactive, have been described (Liptzin and Levkoff, 1992). Delirium is associated with adverse clinical outcomes: increased mortality; increased length of hospital stay; increased rates of institutionalisation; and development of dementia (Siddiqi et al., 2006, Witlox et al., 2010). The adverse outcomes described cause significant morbidity for both the patient and their carers and thus have significant health economy costs (Leslie et al., 2008). This has been estimated, in 2008 and in the United States of America, to cost between \$16 303 and \$64 421 per patient and thus a total cost of \$38 billion to \$152 billion each year (Leslie et al., 2008). This represents an estimated 2.5 fold increase in costs compared to people without delirium.

A Pubmed search using the Medical Subject Headings, or MESH, terms ‘delirium’ with ‘elderly’ or ‘aged’ shows a steady increase in the number of scientific papers published on delirium, illustrated in Figure 1-1. Despite the high prevalence of delirium in hospital and its relative importance in terms of prognosis it still remains under-researched.



**Figure 1-1: Graph of Pubmed citations of Mesh terms 'delirium' and 'aged' since 1980**

In the United Kingdom the introduction of clinical guidelines has helped to highlight the importance of delirium and allow for structured identification and management. The first of these were published by the British Geriatrics Society (British Geriatric Society, 2005). These guidelines focussed on both delirium and dementia, acknowledging the two are closely related and suggested strategies to identify dementia in people with delirium. These guidelines acknowledge that in hospital people are often identified as ‘confused’, a general term that encompasses delirium and dementia among other conditions, including behavioural and psychiatric symptoms seen in dementia. Most commonly it will be delirium or dementia but this is often tricky to distinguish. The National Institute for Clinical Excellence published its first clinical guidelines for delirium in 2010 (Young et al., 2010). These guidelines suggested strategies for identifying delirium by screening those at high risk. High-risk patients included those over 65 years, those with pre-existing dementia, those with severe physical illness and



those with a fractured neck of humerus. Those at high risk, which in reality is the majority of acute admissions, it then suggests are assessed for changes suggestive of the clinical features of delirium. If these are present then formal assessment and/or diagnosis of delirium should take place. The guidelines also include recommendations on treatment and prevention. The guideline was then further revised, in 2014, to include five quality standards that hospitals should be meeting when providing care to people with delirium. These are: 1) Adults newly admitted to hospital or long-term care who are at risk of delirium are assessed for recent changes in behaviour, including cognition, perception, physical function and social behaviour, 2) Adults newly admitted to hospital or long-term care who are at risk of delirium receive a range of tailored interventions to prevent delirium, 3) Adults with delirium in hospital or long-term care who are distressed or are a risk to themselves or others are not prescribed antipsychotic medication unless de-escalation techniques are ineffective or inappropriate, 4) Adults with delirium in hospital or long-term care, and their family members and carers, are given information that explains the condition and describes other people's experiences of delirium, and 5) Adults with current or resolved delirium who are discharged from hospital have their diagnosis of delirium communicated to their GP.

### 1.1.1 Fictional Case Study

A case study is now presented to highlight the issues commonly experienced when managing an older patient with delirium in a hospital setting. This is a fictionalised case, but it is typical of how delirium in older people presents to hospital.

An 80 year old woman, Mrs TJ, is admitted to the hospital by her family who live with her. They say she has not been herself for the previous two days. She has been sleepier and has not wanted to eat or drink very much. She has spent most of the days in her chair, rather than

walking around. They say she cannot hold the string of a conversation together and she appears 'confused'. She is unsure of the time of day and keeps talking about needing to catch a bus to work.

Mrs TJ has a past medical history of hypertension, diabetes and urinary incontinence. She is currently taking bendroflumethiazide 2.5mg OD, ramipril 5mg OD, amlodipine 10mg OD, aspirin 75mg OD, metformin 500mg TDS and oxybutynin 2.5mg OD. The oxybutynin was started at a recent consultation. Her family say that over the past year she has become increasingly forgetful and withdrawn. For the last six months they have taken over her finances as she was having increasing difficulty in keeping these in order.

On assessment in the acute admissions ward, she has normal a temperature of 36.9, a raised heart rate of 95 bpm, a slightly low blood pressure of 109/61 and low oxygen saturations of 92% on room air. Her capillary blood glucose is normal at 5.7 mg/dl. She is sleepy and difficult to wake up. On waking she is unable to say the months of the year backwards and has difficulty maintaining eye contact. Her Abbreviated Mental Test Score (AMTS) is 4/10. She has clinical signs of consolidation (infection) in her right lung base and has evidence of a palpable bladder on abdominal examination. Her blood tests show evidence of infection (C reactive protein 120 mg/L, normal <5 mg/L). A urinary bladder scan shows an abnormal 980ml of residual urine volume.

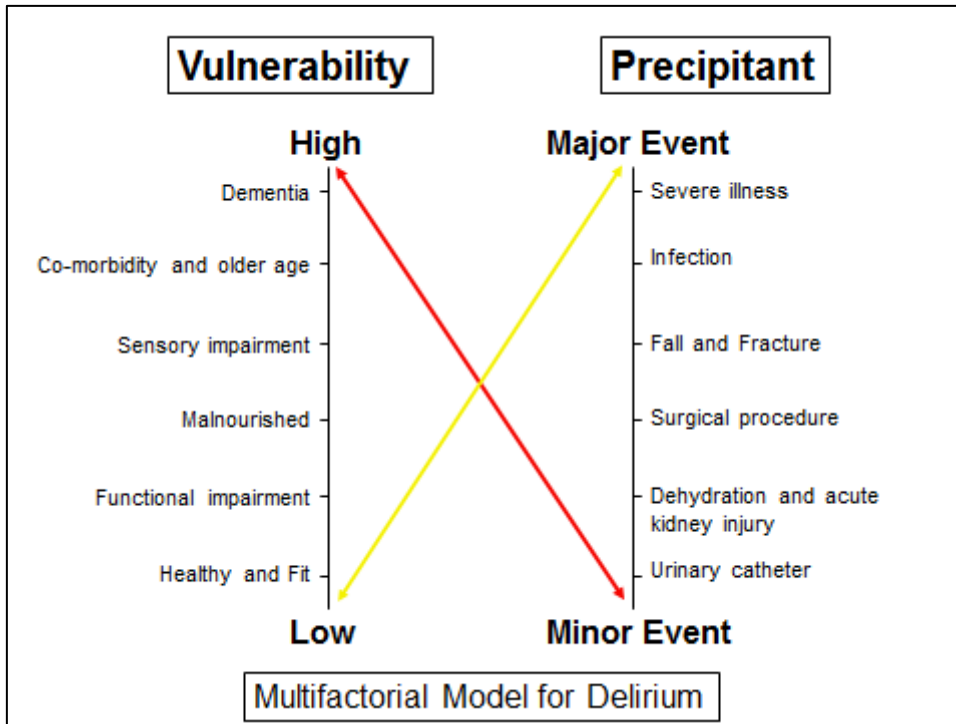
Mrs TJ has hypoactive delirium. Her vulnerabilities to delirium are a background of cognitive impairment and polypharmacy. The potential precipitants of delirium are a new prescription of oxybutynin (an anti-cholinergic drug), urinary retention and pneumonia. The urinary retention may be due to constipation or oxybutynin. As is often the case in frail older people the cause for delirium is likely to be multifactorial. Her treatment at this stage should be to

address each precipitant; stop the oxybutynin, insert a urinary catheter and give antibiotic treatment for the infection and hydration. The urinary catheter and hospitalisation may worsen or prolong the delirium and she is at risk of acute kidney injury given the urinary retention, ACE inhibitory treatment and metformin.

This case illustrates the complexities of the condition and highlights the skilful assessment and management needed to provide high quality care. The case will be revisited later in the thesis to illustrate some key findings of the thesis.

### 1.1.2 Why do older people develop delirium?

Delirium occurs due to the interaction of a patient with specific vulnerabilities and a precipitating event. Any person can develop delirium, but it is most commonly seen in older people. Older people have a higher degree of vulnerability to delirium, so require a less severe precipitating event to cause delirium. In younger people, with less vulnerability, the precipitating event is often more severe. This was conceptualised as a multifactorial risk model (Figure 1-2).



**Figure 1-2: Multifactorial model illustrating the development of delirium. Adapted from Inouye 1993 and Ahmed 2014**

The concept of specific vulnerability risk factors for older people to develop delirium in hospital was first formalised in 1993. A prospective cohort study of older hospital patients identified four independent baseline risk factors for delirium: visual impairment; severe illness; cognitive impairment and renal impairment (raised urea/creatinine ratio) (Inouye et al., 1993). Meta-analysis conducted in 2014 identified dementia, older age, co-morbidity, illness severity, infection, 'high-risk' medication use, reduced function, immobility, sensory impairment, urinary catheterisation, urea and electrolyte imbalance, and malnutrition from 11 studies of older hospital inpatients (Ahmed et al., 2014). Pooled analysis from the studies show the most important risk factor is dementia, with people with dementia having a six times greater risk of developing delirium than those without (OR 6.62, 95% confidence interval 4.30-10.19,  $p < 0.0001$ ).

A number of delirium risk scales have been developed in an attempt to allow appropriate risk stratification and resource allocation. In older medical in-patients a delirium prediction tool identified the presence of any of three risk factors (age over 85 years, high level of physical dependence or use of psychotropic medication) predicting delirium. This had sensitivity of 93.4% and specificity of 60.6% to predict in-patient delirium (Martinez et al., 2012). Scales for the Intensive Care Unit (ICU) (PRE-DELIRIC (van den Boogaard et al., 2012)), cardiothoracic (Rudolph et al., 2009) and vascular surgery units (Pol et al., 2011) are also used.

#### 1.1.2.1 Precipitants of delirium

The precipitant for delirium can be a single event, but the precipitant is often multifactorial events. Precipitants can occur in the community, such as infection or falls, and here the patient presents to hospital with delirium – so called prevalent delirium. The precipitant may also occur during a hospital stay, such as surgery or medication (van den Boogaard et al., 2012), and thus the person develops delirium in hospital – so called incident delirium. In-hospital precipitants for delirium were first described in 1996 and the most common were: the use of physical restraints, malnutrition, the addition of three medications, urinary catheter insertion, and an iatrogenic event (Inouye and Charpentier, 1996). Precipitants in medical inpatients described since also include acute renal impairment (O'Keeffe and Lavan, 1996) and the use of psychotropic medications (Martinez et al., 2012). Other common clinically observed precipitants include urinary retention, pain, falls and fractures, anticholinergic medications, and environmental change.

Vulnerabilities and precipitants are summarised in Table 1-1

**Table 1-1: Identified baseline vulnerability and precipitating events among older hospitalised patients**

Baseline Vulnerability	Precipitating event
Dementia	Infection
Age	Surgery
Co-morbidity and reduced physical function	Acute renal impairment
Immobility	Urinary catheter use
Malnutrition	Psychotropic medication
Sensory impairment	Addition of 3 medications

### 1.1.3 How can delirium be defined?

The term delirium is defined in the Oxford English Dictionary (OED) as:

“A disordered state of the mental faculties resulting from disturbance of the functions of the brain, and characterized by incoherent speech, hallucinations, restlessness, and frenzied or maniacal excitement.”

The word delirium was first recorded in Master Broughton’s letters in 1599 and was included in the first edition of the OED in 1895. A second definition in the OED is that of:

“Uncontrollable excitement or emotion, as of a delirious person; frenzied rapture; wildly absurd thought or speech.”

This was first recorded later in 1650, suggesting the medical term originated first. The etymology of *dēlīrium* is from the Latin for madness, deranged. The noun is derived from the

verb *delir*;, to be deranged, crazy, out of one's wits. This is derived originally from the meaning of going off the furrow (de-away, lira – furrow), to deviate from the straight. The french verb, *délirer* also means ‘to doat, rave, do things against reason’. The term ‘delyre’ was actually recorded earlier in the Coventry Mystery Plays of 1400, with the quote:

“God wyl be vengyd on man that wyl nevyr be schrevyn, but evyrmore doth delyre”

The typical motor symptoms of delirium were first described by Hippocrates (Holt et al., 2014) and the concept of a change in a person’s mental state in the context of illness has been well understood since.

#### 1.1.3.1 Medical definitions and history

Delirium as a medical term was first described in the literature in 1959 (Engel and Romano, 1959) and elegantly described as a syndrome in older people during a key note lecture delivered to the British Medical Association the same year (Bedford, 1959). Delirium was first defined as a diagnosis in the third edition of the Diagnostic and Statistical Manual of Mental Disorders in 1980 and the definition has been expanded further with every edition since. It was first included in the 10<sup>th</sup> edition of the International Classification of Diseases (ICD) in 1990.

Delirium is defined in both the DSM-IV-TR and the 10<sup>th</sup> International Classification of Diseases (ICD-10). The definitions are similar, but the DSM-IV-TR has fewer diagnostic criteria. Both include a disorder of consciousness and attention as the first core feature. The second core feature in both is an acute cognitive change. ICD-10 however only states this to be a disorder of memory, whereas DSM-IV-TR includes disorientation, language, and perception. They both state the change is of sudden onset, there are fluctuations, and that the

delirium is the result of evidence of a co-existing medical condition. ICD-10 adds two further core criteria; psychomotor disturbance and a disturbance in the sleep-wake cycle. Both these symptoms are noted as only associated features in DSM-IV-TR. These diagnostic criteria have been compared directly and DSM-IV-TR would appear to be more inclusive, with 24.9% of acute admissions diagnosed with delirium using DSM-IV and only 10.1% diagnosed using ICD-10 (Laurila et al., 2003). The outcomes are no different between these groups suggesting a more inclusive criterion is better (Laurila et al., 2004). For the purposes of this thesis, the DSM-IV-TR criteria will be used throughout.

Although published after the start of this work, so not used in the thesis, it is worth briefly discussing the important changes in the 5<sup>th</sup> edition of DSM (DSM-5) published in 2013. DSM-5 changes the first core criteria to a disturbance in consciousness and awareness, as opposed to consciousness and attention. It is unclear conceptually how a disturbance in awareness is different to consciousness. The text of DSM-IV-TR defines a disturbance of consciousness as a reduced clarity of awareness of the environment, and the text of DSM-5 defines a disturbance in awareness as a reduced orientation to the environment or to oneself. A recent study comparing DSM-IV and DSM-5 found a strict interpretation of DSM-5 reduced the diagnosis of delirium cases, whereas a more relaxed approach (removing the novel criteria to demonstrate reduced orientation to the environment) led to similar diagnosis rates (Meagher et al., 2014c). What is novel in DSM-5 is that it also requires classification of time course (acute or persistent) and psychomotor subtype (hyperactive, hypoactive or mixed).

In practice however delirium is often not recognised by medical staff. Rates of detection of delirium range from 28% to 72% (Collins et al., 2010, Kales et al., 2003, Fick et al., 2002)



and the reasons for this are not clear (Teodorczuk et al., 2012). This may be because the significance of delirium is not recognised by medical staff, or that the more subtle symptoms associated with hypoactive delirium are truly overlooked.

#### 1.1.4 How does delirium present?

As described in DSM-IV-TR the essential feature of delirium is a disturbance of consciousness accompanied by a change in cognition. It also includes impairment in the ability to focus, shift and sustain attention. These deficits present as symptoms over a few hours to days. The symptoms can also change in nature and severity over the course of the day. It is worth describing these core features in detail.

##### 1.1.4.1 Attentional deficits

Consciousness is an overarching term describing a subjective experience of wakefulness and awareness, and the ability to experience feelings. A disturbance of consciousness is therefore a difficult construct to define. The DSM-IV-TR operationalises disturbed consciousness as an impairment of attention and alertness. Attention consists of three main tasks: orienting to sensory events, detecting signals for focal processing, and maintaining a vigilant or alert state (Posner and Petersen, 1990). Attention is a core component of overall cognitive function, so disorders of attention also result in disorders in other cognitive domains. As a result, inattention is considered the cardinal feature of delirium.

Attentional deficits can be measured at the bedside by both neurocognitive testing and subjective assessment (Tieges et al., 2014). A deficit in attention is core to the main available screening tools for delirium (Inouye et al., 1990, Bellelli et al., 2014b). Typical short bedside tests of attention include retelling the months of the year backwards and a digit span test. Patients with attentional deficits are often distracted, will repeat answers to questions

(perseveration), lose track of conversations and have poor eye contact. Indeed simple bedside testing of attention using the months of the year backward alone may detect delirium (O'Regan et al., 2014)

#### 1.1.4.2 Acute cognitive deficits

An acute change in cognition is the second core feature of delirium. The most typical cognitive deficit is in short term memory. A person may forget where they have put things or what is going on during the day. Direct assessment will result in poor scores on a range of cognitive tests such as the abbreviated mental test score (AMTS). Commonly people also appear disorientated, not knowing where they are or what time of day it is. More subtle cognitive deficits may include changes in the way a person processes space and vision (visuospatial) and could lead to a person falling. The person with delirium may have altered perception, causing misunderstanding in the use of day-to-day objects, or misunderstand the meaning of conversations. Their speech and thought may appear disorganised. All these may be seen in dementia, but it is the acuteness of the symptoms, or worsening of symptoms from an established baseline, that are seen in delirium.

#### 1.1.4.3 Motor subtypes

Delirium is also commonly associated with disturbance in motor function and this presents with two distinct motor subtypes (Liptzin and Levkoff, 1992). Hyperactive delirium presents with increased motor activity, observed as agitation, often pressured speech and wandering. Hypoactive delirium presents with reduced motor function, observed as slowing of movement, speech and withdrawal. In some patients, both motor subtypes are observed and they are classified as having mixed delirium (O'Keeffe and Lavan, 1999). Various classifications of motor subtype when applied to the same patients only showed agreement in

34% of patients (Meagher et al., 2008). With this in mind a clinical scale was developed, the Delirium Motor Subtype Scale (DMSS). This has been further refined into a shorter version the DMSS-4 (Meagher et al., 2014a). Although motor subtype is a clinically observed phenomenon, motor subtypes have been studied objectively using accelerometers (Godfrey et al., 2009). This approach has also been used to validate the DMSS (Godfrey et al., 2010).

The significance of classifying motor subtypes remains unclear, with conflicting reports describing differing prognosis related to each subtype: with hyperactive delirium conferring worse prognosis (Marcantonio et al., 2002) in a cohort of hip fracture patients, but hypoactive delirium conferring worse prognosis in post acute care patients (Kiely et al., 2007). To date, there has been no research examining motor subtypes and their relationship to pathophysiology.

### 1.1.5 Why is delirium important? – Epidemiology

Delirium is important clinically because it is both common and related to adverse clinical outcomes. The following sections will describe this in more detail.

#### 1.1.5.1 Population based epidemiology

The prevalence of delirium in the community is hard to define. Three studies report the community based point prevalence of delirium is between 0.63% and 1.09%. Meta-analysis has reported a pooled prevalence of 0.72 % (CI 0.48-0.96) from a total of 5121 participants aged 65 years and over (Davis et al., 2013). A further study reports the period prevalence of 10% over 5 years. It is worth noting that the largest study reporting point prevalence excluded those with dementia, and in the study where dementia was explicitly defined the point prevalence is 7.9% in people with dementia. This suggests that at any one time one in

12 people with dementia will have delirium. Therefore, the true figure is likely to be higher than that reported in the meta-analysis.

In care homes the prevalence is much higher, ranging from 6.5% to 70.3% (de Lange et al., 2013). The higher prevalence rates are in care homes specifically for people with dementia, and higher care home rates represent the higher baseline vulnerabilities to delirium seen in this population. One of the difficulties with interpreting care home prevalence rates is how different countries define what a care home is. In North America, care homes tend to have higher levels of medical input than in Europe, akin to community hospitals in the UK. In European care homes, the prevalence is between 6.5%, in a Swiss care home with low rates of dementia (von Gunten and Mosimann, 2010); through 24.9 % in a Finnish care home (Laurila et al., 2003); and 58%, in a Swedish care home with dementia prevalence of 66% (Sandberg et al., 1998).

#### 1.1.5.2 Hospital based epidemiology

Delirium is common among older people in hospital. As already described, people admitted to hospital with delirium are traditionally described as prevalent delirium cases. People who are already admitted to hospital, but develop delirium during the course of the in-patient stay, are described as incident delirium cases. A systematic review of the occurrence and outcomes of delirium in older medical inpatients was published in 2006 (Siddiqi et al., 2006). This identified 40 separate delirium cohorts reported in 42 published papers, 21 reporting delirium prevalence, 13 reporting the incidence of new delirium and 13 reporting occurrence rates of delirium. This systematic review has been used as a basis for reporting the occurrence of delirium in older medical patients, with a further description of studies published since this review.

#### *1.1.5.2.1 Prevalent delirium*

This thesis is primarily concerned with older people admitted to hospital with delirium – prevalent delirium, or community acquired delirium. Emergency departments are often the first point of admission of older people to hospital. In emergency departments, the prevalence of delirium among older people is reported to be between 8% and 10% (Han et al., 2010)

A systematic review reported prevalence among older people admitted to hospital of between 10% and 31% (Siddiqi et al., 2006). Since that review was published in 2006, a further nine studies report the prevalence of delirium among older people admitted to hospital. Prevalence ranges between 15.6% and 34.6% and these are described in Table 1-2. Strengths of these studies are that they are representative of older people admitted to general hospital, with typical average age and gender values. However, only three studies used reference criteria (DSM-IV) to diagnose delirium, reporting a prevalence of 28.8% and 25.9%, as opposed to a validated screening tool. A pooled prevalence of 20.3% (388/1663) is also reported in Table 1-2

A point prevalence study of delirium was conducted in a general hospital in Ireland. Trained assessors attempted to screen and diagnose delirium in patients over 18 years of age across the whole hospital (excluding ITU) in a single day (Ryan et al., 2013). They reported a point prevalence of delirium (DSM-IV) of 19.5%, with this rising to 21.3 % in the 65-79 years old age group and 34.8% in the over 80 age group.

**Table 1-2: Details of studies describing the prevalence of delirium in older acute admissions. CAM = Confusion assessment method, DSM-IV= Diagnostic and Statistical Manual for Mental Disorders version 4**

Study	Setting	Patients	Prevalence	Ascertainment
(White et al., 2005)	Unselected admissions	medical >75yrs 82yrs, 59% female	76/283 26.8%	DSM-IV Geriatrician
(de Rooij et al., 2007)	Academic hospital Unselected admission	>65years 80, 58% female	64/185 34.6%	CAM Physician
(Adamis et al., 2006)	University hospital Geriatric admissions	>70year 82.8±6.5, 59.6% female	27/94 28.7%	CAM Experienced clinician
(Iseli et al., 2007)	General hospital Medical admissions to geriatric medical unit	>65 yrs 80yrs, 59% female	19/104 18%	CAM Physician
(Collins et al., 2010)	Teaching Hospital Unselected admissions	>70yrs 83 , 59% female	110/710 15.5%	CAM Old age psychiatrist
(Eeles et al., 2010)	District general hospital Unselected admissions	>75yrs 82.3±7.5, 63.1% female	80/278 28.8%	DSM-IV Geriatrician
(Buurman et al., 2011)	2 University hospitals Unselected general medical admissions	>65yrs 78 yrs, 54% female	118/622 19.0%	CAM Nurse and geriatrician
(Wierenga et al., 2012)	University hospital Unselected general medical admissions	>65 yrs 78yrs, 53% female	166/641 25.9%	DSM-IV geriatrician
(Whittamore et al., 2014)	University hospital Unselected admissions (medicine, geriatric medicine, orthopaedics)	>70yrs 84yrs, 66% female	107/396 27%	DRSR-98 nurses or psychology graduates Subset diagnosed by clinician
Pooled			388/1663 20.3%	

#### *1.1.5.2.2 Incident delirium*

Incident delirium is seen in people already admitted to hospital and could be conceptualised as hospital acquired delirium. This thesis will examine prevalent delirium but will briefly describe the epidemiology of incident delirium.

A systematic review of studies reporting the incidence of delirium in older medical patients reports delirium incidence ranging from 3% to 25% during the in-patient stay. Since this review, seven studies have reported an incidence between 11% and 29%. Incident delirium is common after surgical procedures. Incidence is up to 46% in cardiac surgery, 50% in non-cardiac surgery and 51% in orthopaedic surgery. In intensive care settings, again there is a wide reported prevalence and incidence with a reported range of 20-80%.

The epidemiology of delirium is summarised in Table 1-3

**Table 1-3: Summary of the epidemiology of delirium in older people. Adapted from Siddiqi 2006, de Lange 2013, Davis 2013, Inouye 2014.**

	Setting	Epidemiology	No of studies
Community	General community	0.63%-1.09%	3
	Long term care	6.5-70.3%	15
Hospital	Prevalence		
	Older Emergency Departments patients	8-17%	3
	Medical inpatients	10%-31%	8
	(Systematic review 2006)		
	Medical inpatients	18%-35%	9
	Incidence		
	Medical inpatients	3%-25%	14
	(Systematic review 2006)		
	Medical inpatients	11%-29%	7
	Orthopaedic surgery	12%-51%	10
	Non-cardiac	13%-50%	4
	Cardiac Surgery	11%-46%	4
	ICU	19%-82%	10



### 1.1.6 Why is delirium important? – Outcomes

Delirium was initially thought of as a benign condition, but has since been shown to be consistently associated with adverse health outcomes. Clinically important outcomes that have been studied are mortality, new institutionalisation, dementia, and hospital length of stay (LOS). In a systematic review in 2006 (Siddiqi et al., 2006) in-hospital mortality from 10 studies reported a wide range from 14.5% to 37%. The review reports mean length of hospital stay from 11 studies ranging from nine to 32 days, with four showing a significant increase in LOS in those with delirium.

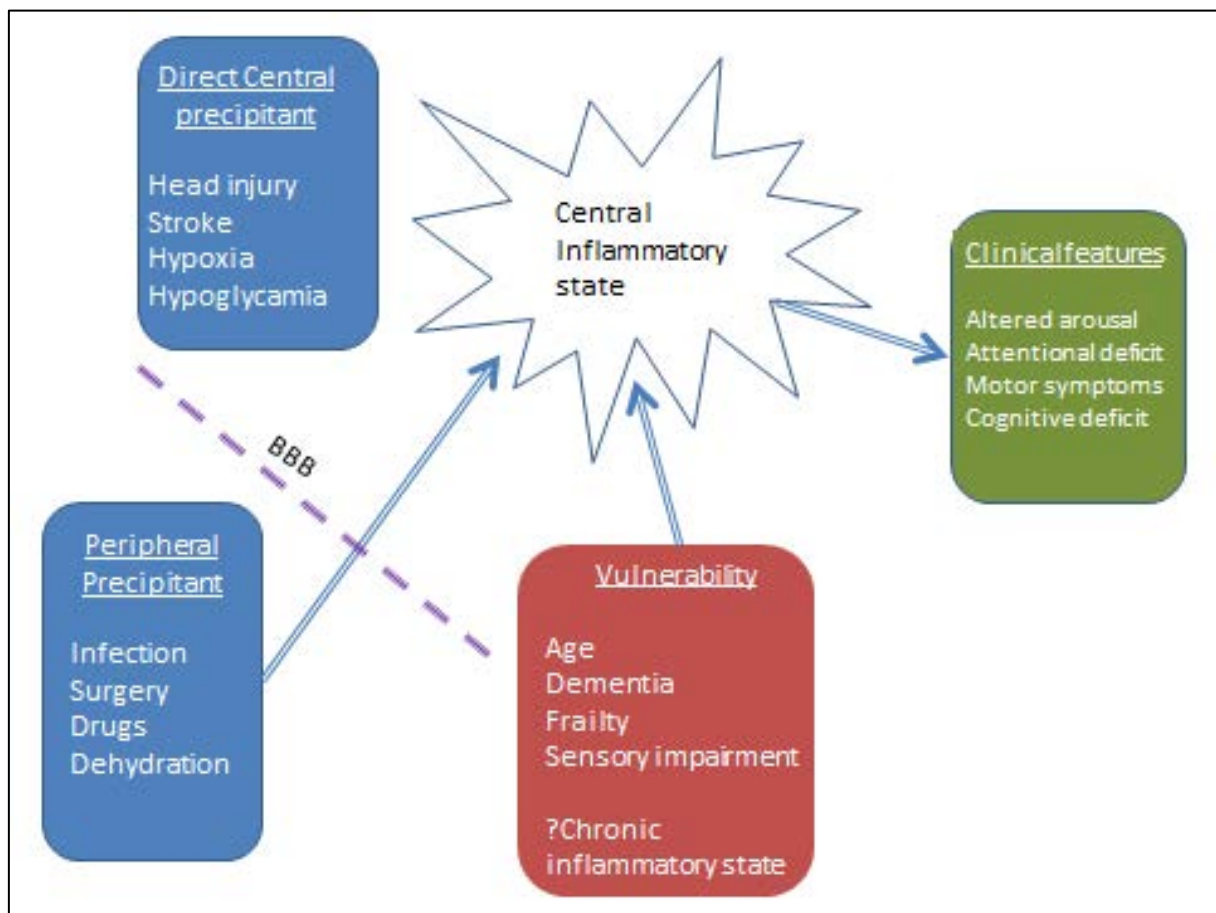
Outcome studies in older people with delirium are difficult to interpret as they are often confounded by dementia and severe illness. Controlling for these in survival analysis can be difficult. An influential systematic review and meta-analysis, published in 2010, identified 51 articles reporting on outcomes in older people with delirium (Witlox et al., 2010). Of these 51 articles only 42 were considered of high quality by the authors. Of those 42 studies, 23 reported statistically adjusted outcomes, of which 16 met the author's criteria for adequate adjustment (statistical control for age, sex, co-morbid illness and illness severity as co-variables). Four articles did not allow for extraction of data for meta-analysis so 12 studies provided data for meta-analysis of mortality as a primary outcome. Seven studies provided data for meta-analysis of new institutionalisation as a primary outcome. For mortality, seven studies provided hazard ratios (HR) and five provided odds ratios (OR), with 1197 of 5023 participants having delirium. Meta-analysis demonstrates a hazard ratio (HR) of 1.95 (95% CI 1.51-2.52) of death at an average of 22 months follow-up. For new institutionalisation, 527 of 2579 participants had delirium, and the OR was 2.41 (95% CI 1.77-3.29) for new institutionalisation at an average follow-up of 15 months.

However, the outcome studies in the meta-analysis by Witlox and colleagues demonstrate quite a wide heterogeneity. HRs reported for mortality range from 1.28 to 4.04, and for new institutionalisation, from 0.93 to 3.29. Although meta-analysis attempts to pool data across studies, it may be that there are other factors accounting for the heterogeneity in outcomes that have yet to be explored. The adverse outcomes seen in delirium are due to a number of reasons. Firstly the underlying aetiology of the delirium may drive adverse outcomes, but direct complications of delirium such as poor compliance with treatment, immobility and falls will play a part. Potential neurotoxicity of delirium also plays a role. As well as this, the complex interplay between precipitants and vulnerability suggests that both the syndrome and its outcomes may not always be the same. Studying differences between patients with good outcomes and those with adverse outcomes may help to inform the understanding of delirium. Studies investigating inflammatory profiles in delirium have conflicting results, so it would be feasible to suggest that there may be different inflammatory and clinical profiles between outcome groups; those who recover from delirium, and those who have adverse outcomes such as death, institutionalisation and cognitive decline.

### 1.1.7 What causes delirium - Pathophysiology of delirium

Despite its importance and prevalence, the pathophysiology of delirium is under researched (MacLulich et al., 2013). This has led to the current partial understanding of the underlying pathophysiology of delirium and to date no unifying pathological mechanism has been described. Delirium is caused by the interaction of background vulnerability with a precipitant leading to a central inflammatory response. Vulnerabilities interact with precipitants, which are often multifactorial, so it is likely a number of pathways play a role. Precipitants are often conceptualized into direct central insults and peripheral insults. Central precipitants, such as head injury or hypoglycaemia, lead directly to neuronal cell disruption.

Peripheral precipitants, such as infection or surgery, cause neuronal cell disruption through interaction with central neurones – so called immune to brain communication. Both these mechanisms lead to a central inflammatory response. This leads to the neurotransmitter imbalance that is responsible for the clinical features seen in delirium. In simpler terms, delirium is a neuropsychiatric syndrome caused by neuronal dysregulation secondary to systemic disturbance (Maldonado, 2013). Figure 1-3 attempts to model this in terms of clinical features of delirium.



**Figure 1-3: Schematic representation of the interplay between precipitant and vulnerability causing delirium. BBB = blood brain barrier**

### 1.1.7.1 Peripheral Inflammation

The most common precipitants of delirium are infection and surgery. Both these insults lead to the activation of a peripheral inflammatory cascade, with increased systemic cytokine production by activated immune cells such as macrophages (Barton, 2008). The pro-inflammatory cytokines (mainly  $\text{TNF}\alpha$  and  $\text{IL}1\beta$ ) initiate local cell change and activation as well as recruitment of leucocytes which contribute to resolution of the inflammation through phagocytosis of pathogens or cell debris. The subsequent action of anti-inflammatory cytokines, such as  $\text{IL}10$ , control tissue damage by effecting resolution of the inflammation. Evidence for an exaggerated peripheral inflammatory cytokine response in delirium was first reported in 2007, with serum  $\text{IL-6}$  and  $\text{IL-8}$  being significantly raised in patients developing delirium in an acute hospital population (de Rooij et al., 2007). Further positive associations between delirium and the pro-inflammatory cytokines  $\text{IL-1}\beta$  (Capri et al., 2014),  $\text{IL-6}$  (van Munster et al., 2008, van Munster et al., 2010, MacLulich et al., 2011, Capri et al., 2014, Liu et al., 2013) and  $\text{IL-8}$  (van Munster et al., 2008) have been reported, though some reports have found no association (Lemstra et al., 2008, Rudolph et al., 2008, Cerejeira et al., 2012) with most inflammatory cytokines measured. A clear association between delirium and the ratio of pro and anti-inflammatory cytokine has been reported. This is to gauge overall inflammatory status, and is expressed as  $\text{IL-10}/\text{TNF}\alpha + \text{IL6} + \text{IL8}$ , suggesting cytokine imbalance, rather than just simply altered levels, may play a role (Cerejeira et al., 2012). The anti-inflammatory cytokines  $\text{IL-1RA}$  and  $\text{IGF-1}$  were reduced in association with delirium amongst a medical inpatient population (Adamis et al., 2009); again suggesting that an imbalance, as opposed to simply a raised inflammatory profile may be significant. Raised peripheral chemokines have also been associated with delirium in a population of patient undergoing cardiac surgery

(Rudolph et al., 2008), suggesting CCL2 may be the primary chemokine involved. These studies are summarised in Table 1-4.

**Table 1-4: Relationships shown between peripheral cytokines and delirium. (2 pages)**

Study and setting	n delirium /n total	Age	%♀	Sample	TNF $\alpha$	IL-1 $\beta$	IL-6	IL-8	IL-10	Other
Capri et al 2014 elective and emergency surgery	37/74	79.2	unk	Pre-op ELISA	✗	✗	✓	✗	✗	Reduced IL-2
Liu et al 2013 Non-cardiac surgery	50/338	71	43	Day 1 post-op ELISA			✓			
Cerejeira 2012, 2014 Elective hip surgery	37/101	73	50	Pre-op Multiplex	✗	✗	✗	✗	✗	Imbalance of pro and anti- inflammatory cytokines
MacLulich et al 2011 Hip # surgery	15/36	62-93	unk	Pre-op Multiplex	✗		✓	✗		
Van Munster et al 2010 Hip # surgery	62/120	84.8	84	Day 3 post-op Multiplex			✓	✗		
Adamis 2009, 2007 Medical inpatients	28/67	84.2	unk	Day 1 ELISA	✗	✗	✗			Reduced IL- 1RA and IGF-1

Table 1 4: Relationships shown between peripheral cytokines and delirium. (2/2 pages)

Study and setting	n delirium /n total	Age	%♀	Sample	TNFα	IL-1β	IL-6	IL-8	IL-10	Other
Van Munster et al 2008 Hip # surgery	50/98	84.6	87	Pre-op multiplex			✓	✓		
Lemstra et al 2008 Hip # surgery	18/68	84.6	55	Pre-op ELISA			×			
Rudolf et al 2008 Surgical ptns	12/42	74.7	8	Day 1 post-op Multiplex	×	×	×	×	×	Increased CCL2
De Rooij et al 2007 Medical inpatients	64/185	80	58	36 hrs post admission Multiplex	×		✓	✓	×	

All studies compare cytokine levels between groups with and without delirium. Significant difference indicates higher levels in the delirium group. Blank cells indicate the cytokine was not measured. ✓ represent where a significant difference is found, and x where no association was found.

C reactive protein (CRP) is a common clinically utilised marker of the peripheral inflammatory response. It is an acute phase protein and has actions similar to pro-inflammatory cytokines. As with cytokines, there are conflicting reports of the relationship between raised CRP and delirium. In a cohort of older acute medical admissions CRP was strongly associated with delirium (Ritchie et al., 2014). Interestingly, in subgroup analysis by admission diagnosis, this relationship was only present in the musculoskeletal disease subgroup, rather than the cardiac, infection or metabolic group. Other reports have confirmed this finding of high CRP levels and an association with delirium (Macdonald et al., 2007, White et al., 2008, Morandi et al., 2007) but some have found no relationship (Cerejeira et al., 2013). This suggests further complexity in the relationship between CRP and delirium.

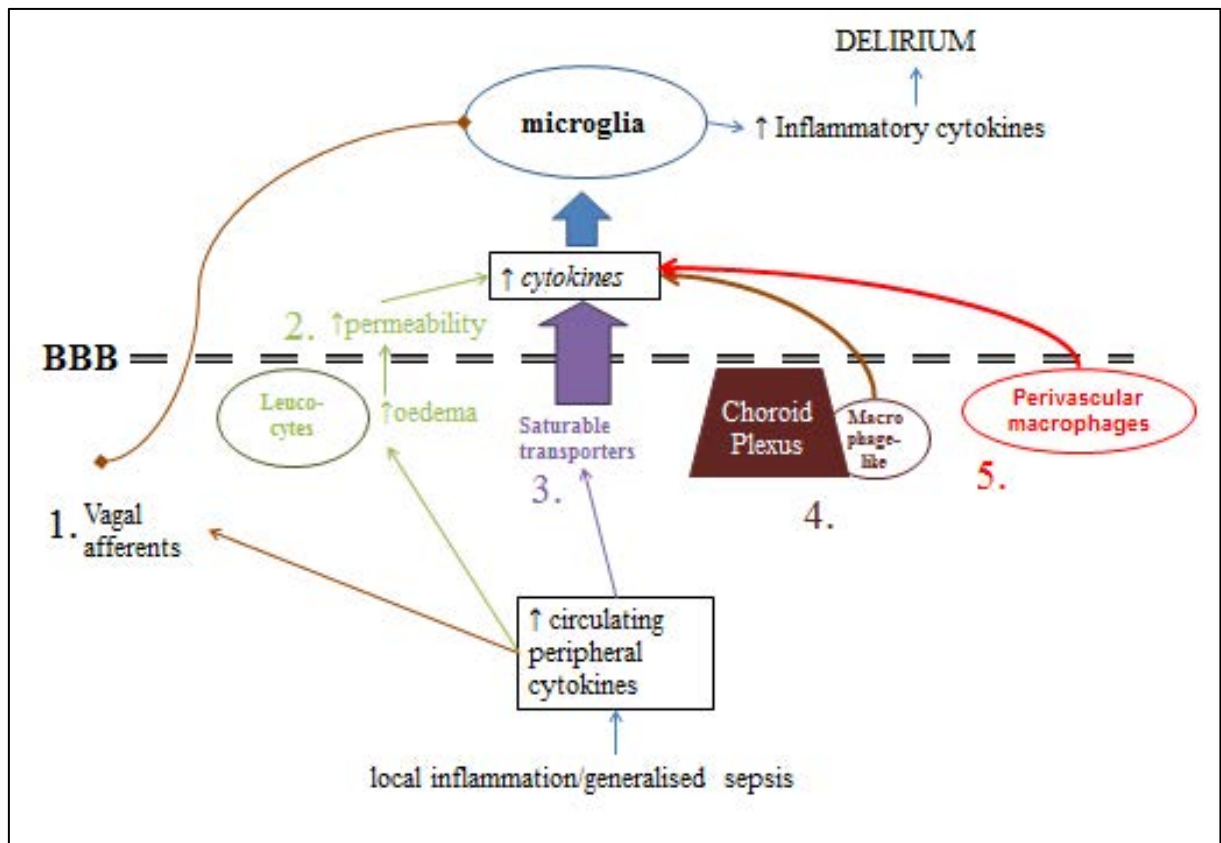
#### 1.1.7.2 Immune to brain communication

The link between peripheral inflammation and central inflammation, so called immune to brain communication, is key to the understanding of delirium. The blood brain barrier (BBB) is a specialised diffusion barrier that is seen as protecting the brain from peripheral insults (Ballabh et al., 2004) and causes the brain to be described as an “immune privileged” site. Disruption of the BBB has been implicated in the development of delirium (Maldonado, 2008) and plays a role in the interaction between peripheral precipitants and the brain. Five pathways of immune to brain communication through the blood brain barrier have been proposed – 1) activation directly through the BBB via vagal neuro-humeral pathways, 2) increased BBB permeability, 3) activation of macrophage like cells at the choroid plexus and circumventricular organs, 4) high concentrations of circulating peripheral cytokines gaining access through saturable transporters, and 5) perivascular macrophages producing local inflammation (Dantzer et al., 2008). Ultimately, these mechanisms cause pro-inflammatory cytokine production by microglial cells within the CNS.



The BBB is made up primarily of endothelial cells, and the interaction of leucocytes with this endothelium leads to increased permeability (Abbott et al., 2010). Cytokines released in the inflammatory response stimulate endothelial cells to express selectins and integrins to cause leucocyte adhesion to the BBB. Activation of the leucocytes (initially neutrophils) causes degranulation and reactive oxygen species (ROS) production which leads to perivascular oedema and subsequent increased BBB permeability. Activation of peripheral vagal nerve afferents by circulating cytokines, typically in the abdomen or lung, are a second route of immune to brain communication. Their activation not only leads to microglial production of cytokines, but also the activation of efferent reflexes potentiating peripheral inflammation. Circulating pathogen associated molecular patterns (PAMPs), derived from microbes, or damage associated molecular patterns (DAMPs) arising from damaged cells or tissue, can activate macrophage like cells at the choroid plexus and the circumventricular organs. The choroid plexus is a peripheral capillary bed that projects into the cerebral ventricles. Its primary function is to produce CSF but it contains macrophage like cells that can produce inflammatory cytokines that enter the CNS by diffusion into the CSF. The circumventricular organs are also peripheral capillary beds that surround the cerebral ventricles and allow immune to brain communication in similar ways. Perivascular macrophages and endothelial cells are activated via IL-1 receptors to produce local prostaglandins and subsequent local inflammation. This local inflammation can then trigger central inflammatory responses (Dantzer et al., 2008).

These mechanisms are summarised in Figure 1-4



**Figure 1-4: Diagrammatic representation of the five type of immune to brain signalling described**

Recently another mechanism of immune to brain communication has been proposed, the ‘glymphatic’ system (Louveau et al., 2015). These are functional lymphatic vessels in the meninges of the brain, allowing lymphatic drainage of the central nervous system into cervical lymph nodes. It is plausible that these vessels also allow the message of macromolecules in to the CNS. However, more research is needed to establish this system’s role in CNS pathology.

S100 $\beta$  is a protein with cytokine properties that is mainly derived from activated astrocytes and is reported to be a marker of both neuronal damage and BBB disruption. As such, it has gathered interest as a potential biomarker for aberrant immune to brain communication and subsequent delirium. S100 $\beta$  has been reported as elevated in both the serum of medical

patients with delirium (van Munster et al., 2010) and ITU patients with delirium (van den Boogaard et al., 2011). Higher S100  $\beta$  is associated with a longer duration of delirium in ITU patients (Khan et al., 2013). Raised central S100  $\beta$ , as measured in the cerebrospinal fluid (CSF) of hip fracture patients, is also associated with delirium (Hall et al., 2013).

#### 1.1.7.3 Microglial cells

Microglial cells are the resident innate immune cell in the central nervous system (CNS) and as such have a crucial role to play in the understanding of delirium. Not only do they act to allow 'immune to brain communication' but they are also responsible for the subsequent neuroinflammation. Microglia account for 16% of CNS cells in humans and are a dynamic cell, existing in both a quiescent state and a primed state. Their main role is in immune surveillance of the CNS and in co-ordinating the CNS response to peripheral immune signalling (Hanisch and Kettenmann, 2007). Microglial cells are described in three phenotypes; quiescent, primed and activated. Quiescent microglia are typically ramified in appearance and make up the majority of the CNS microglial population. Peripheral and central signalling switches the microglial morphology to a primed state and subsequently from a primed to an activated state. Activated microglia then propagate inflammation through release of IL-1 $\beta$ , TNF $\alpha$  and IL6. This activation is then resolved through anti-inflammatory stimuli and they return to their quiescent state (Cunningham, 2013).

In states of vulnerability to delirium, age and neuroinflammation, there is both an increase in the primed microglial population as well as a hyperactive response to activation. The exaggerated neuroinflammation seen in response to both central and peripheral stimulation of microglia could be explained by the increased inflammatory profile seen in normal ageing ("inflammageing"), which gives the older adult a raised basal state of inflammation before

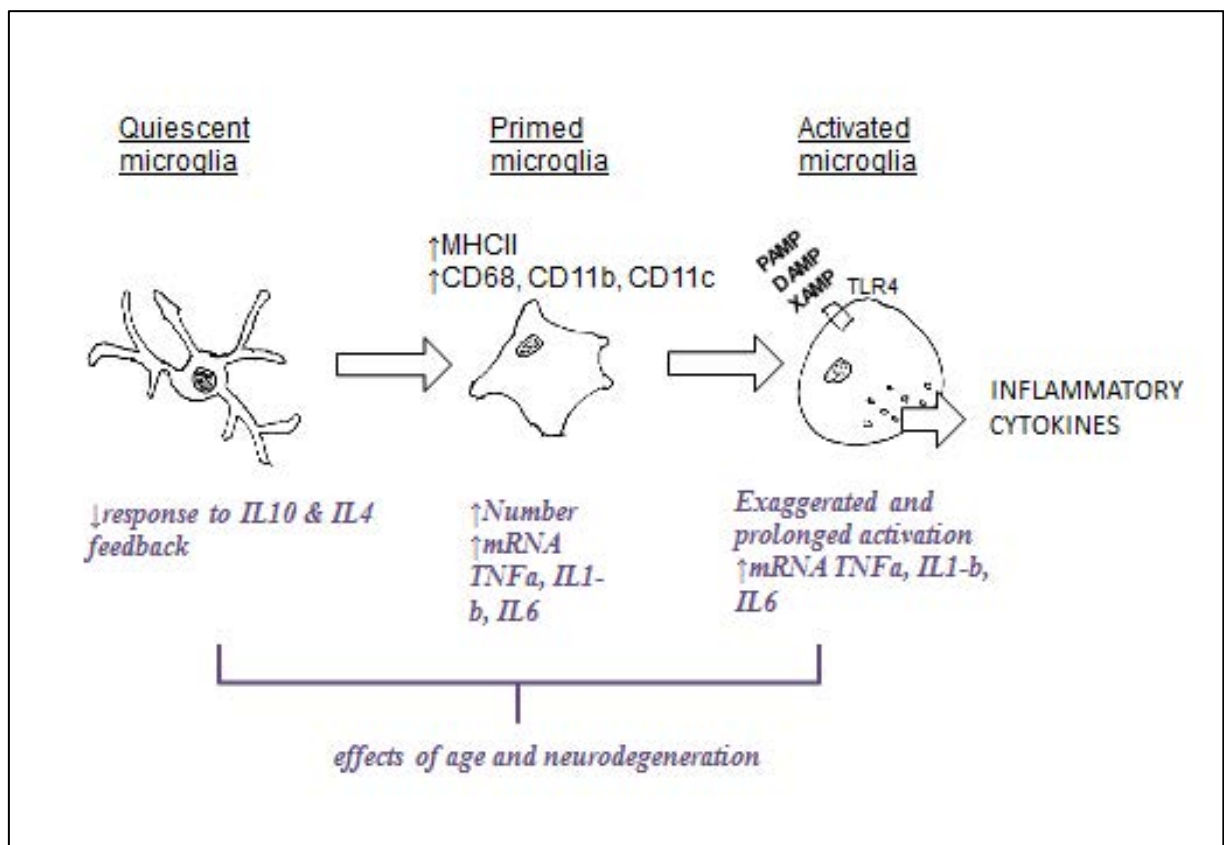
any precipitant is encountered (Franceschi et al., 2007). Primed microglia have a higher expression of major histocompatibility complex II (MHCII), with 25% of microglia expressing this in aged mice, compared to just 2% in adult mice (Henry et al., 2009) as well as increased inflammatory markers such as CD68 (a scavenger receptor), TLRs, CD11b and CD11c (both integrins) (Norden and Godbout, 2013). Aged mice also show an increase in microglial mRNA for both pro-inflammatory cytokines (TNF $\alpha$ , IL-1 $\beta$  and IL-6) and the anti-inflammatory cytokine IL-10 (Sierra et al., 2007).

Microglial cells are activated through toll-like receptor 4 (TLR4) to release pro-inflammatory cytokines (Jalleh et al., 2012). Cellular injury causes a release of the TLR4 activators DAMPS, and infections lead to the ligation of TLR4 by PAMPS. Drugs that typically cause delirium, such as opiates, are associated with circulating xenobiotic-associated molecular patterns (XAMPs) which are also an activating ligand for TLR4. In age and neurodegeneration this activation is both exaggerated and prolonged, resulting in an increase in released cytokines. This is seen as a higher production of CNS IL-1 $\beta$  and IL-6 in aged mice when stimulated with peripheral LPS, as well as evidence of prolonged stimulation (Godbout et al., 2005). Increased IL-1 $\beta$  and neuroinflammation was reported in aged, but not adult mice in response to minor abdominal surgery (Rosczyk et al., 2008). The activation is prolonged, with raised IL-1 $\beta$  seen for up to 24 hours after LPS, only in aged mice (Wynne et al., 2010). Microglial activation is seen in Alzheimer's disease (AD) and prion disease, with increased microglial IL-1 $\beta$  seen post LPS challenge in mice with a model of AD compared to controls (Cunningham et al., 2005).

Microglia are subsequently 'turned off' by the action of IL-10, which acts to regulate IL1 $\beta$  production and return the microglial cell to the quiescent state. Increased microglial IL-10 is

seen following LPS stimulation (Henry et al., 2009) but it is unclear why this is then not effective in reducing CNS inflammation and this may suggest that there is an impaired brain response to IL-10 with age. It may be that aged microglia express less IL-10 receptor or signalling is reduced and thus the increased IL-10 is not as effective. IL-4 is another anti-inflammatory cytokine that acts in a similar way on microglia. Adult mice, as opposed to aged mice, are able to up-regulate the IL4 receptor in response to LPS and thus aged mice have impaired sensitivity to IL-4 (Fenn et al., 2012).

Some caution is required as the studies of microglial response in this area are all rodent based, and there is no current direct evidence of microglial priming in humans.



**Figure 1-5: Microglia activation and the effects of age and neurodegeneration**

#### 1.1.7.4 Central Nervous System in humans

Because of the relative inaccessibility of the CNS in humans there is less known about CNS inflammation than peripheral inflammation in delirium. The human CNS can be accessed at death by post mortem examination, and in vivo through cerebrospinal fluid sampling by lumbar puncture.

##### *1.1.7.4.1 Post-mortem studies*

There have been two post mortem studies of delirium. A case series of seven patients with delirium from an intensive care unit demonstrated an increase in ischaemic lesions, particularly in the hippocampal area (Janz et al., 2010). A case control study comparing nine cases of delirium with six matched controls demonstrated higher markers of microglial activation (CD68) and higher IL-6 immunoreactivity in the delirium group, as well as higher markers of astrocyte activity (Munster et al., 2011).

##### *1.1.7.4.2 Cerebrospinal fluid studies*

Cerebrospinal fluid (CSF) is taken from within the dural space and is considered part of the central nervous system. Measurements of inflammatory cytokines in the CSF offer a valuable insight into the central inflammatory response in delirium. However, CSF is usually sampled by lumbar puncture, and this is often very difficult to perform in patients with delirium, and carries significant burden. Therefore the majority of studies examining CSF are from surgical cohorts as spinal anaesthesia allows an opportune time to sample CSF with little added burden. A systematic review of CSF studies in delirium identified eight studies (total 235 patients) reporting 17 different biomarkers (Hall et al., 2011). Delirium is reported as being associated with the following CSF biomarkers: elevated IL-8, serotonin metabolites, cortisol and lactate, and reduced somatostatin, beta-endorphin and neuron-specific enolase. However,

the patients studied were very heterogeneous and offered little insight into the neuropathophysiology of delirium. Thus the authors reported conclusions could not be drawn. A more recent study of CSF from patients with hip fracture reported an increase in IL-8, but null associations with TNF- $\alpha$ , IL-10 and IL-1 $\beta$  (MacLulich et al., 2011). This study also reported undetectable levels of serum IL-8 suggesting the IL-8 is CNS derived. A similar study, again of hip-fracture patients, showed reduced CSF IL-1RA, an anti-inflammatory cytokine, and reduced IL-6, a pro-inflammatory cytokine, in those who subsequently developed delirium post-surgical repair (Westhoff et al., 2013). IL-1 $\beta$  is raised in the CSF of those with delirium and hip fracture, but there is no correlation with serum IL-1 $\beta$ , again suggesting the production is from the CNS (Cape et al., 2014). This study reported raised IL-1RA in those with delirium on admission with hip fracture compared to those whose developed delirium after repair. IL-1RA is produced in response to IL-1 $\beta$ , suggesting the IL-1 $\beta$  rise occurs early on in the development of delirium. This indicates CNS inflammation, as demonstrated by raised CSF cytokines, is a predictor of risk of delirium in the post-operative period.

#### 1.1.7.5 Animal Models

Given the relative inaccessibility of the CNS, it may be that animal models of delirium allow all these separate strands to be joined together. The first animal model in delirium used atropine, an anti-cholinergic drug, as a pharmacological cause of delirium in rats. Atropine was administered to one group and the other group was given a placebo. Signs and behaviours were noted during observation and water maze tasks similar to that of delirium in the group given atropine. The atropine group also demonstrated typical EEG slow waves that are associated with delirium (Trzepacz et al., 1992).

To investigate microglial activity and cytokines from blood and brain in young and aged mice, the mice were challenged with either intra-peritoneal lipopolysaccharide (LPS), as a proxy of peripheral systemic infection, or saline. In the aged mice there was a reduction in observed social behaviour and loco-motor activity akin to hypoactive delirium (Godbout et al., 2005). The aged mice also had attenuated brain IL-6 and IL-1 $\beta$  post LPS challenge compared to the young mice.

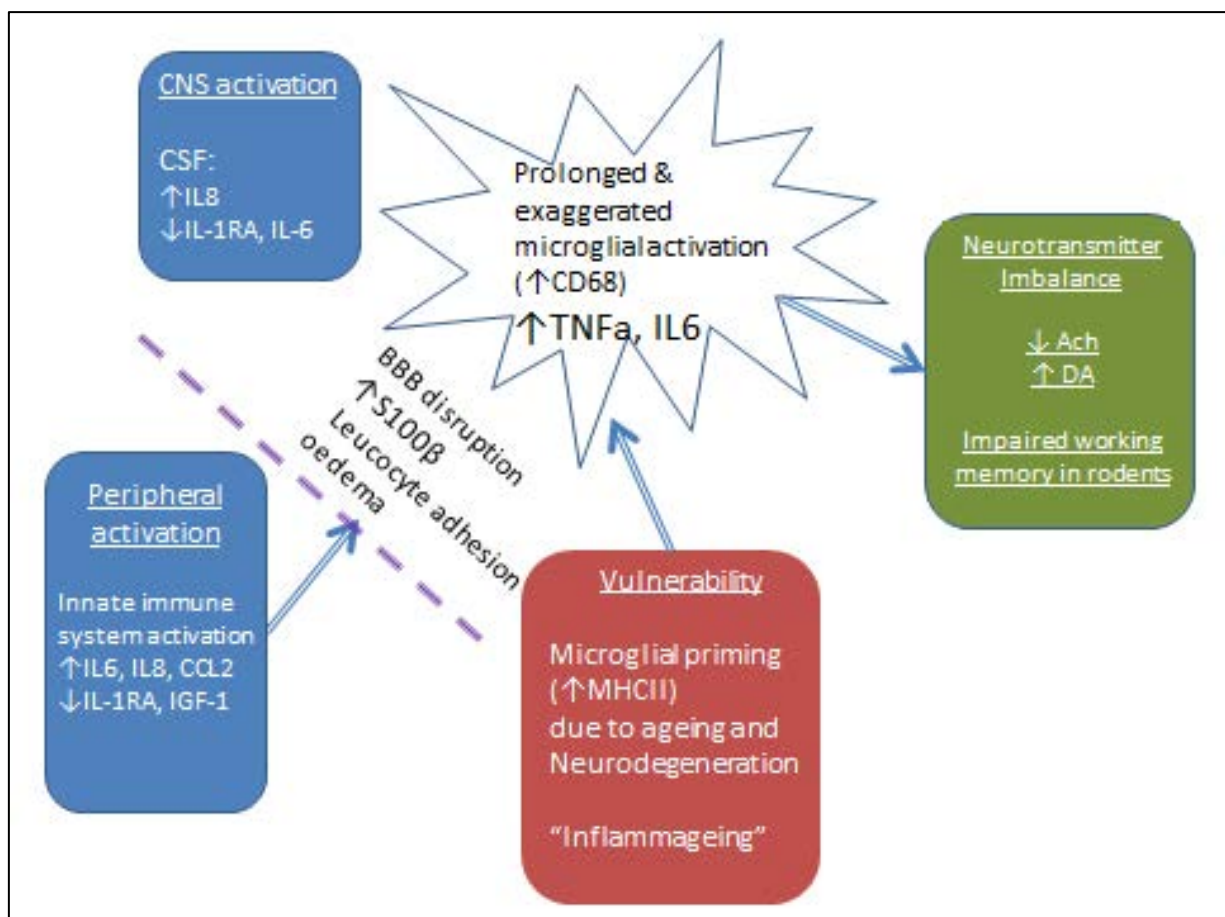
Working memory deficit, as a proxy for delirium, was tested in adult and aged mice post sham abdominal surgery. A Morris water maze was used and hippocampal cytokines measured. Both adult and aged mice displayed evidence of impaired working memory. However, the aged mice showed signs of greater perseveration and greater neuroinflammation, with increased hippocampal IL-1 $\beta$  (Rosczyk et al., 2008).

The most complete mouse model for delirium demonstrates evidence of both microglial priming, and over activation in mice with existing neurodegeneration after challenge with LPS (Cunningham et al., 2005). Mice were treated with ME7, a prion disease strain that causes primarily hippocampal disease characterised by amyloidosis and cognitive decline. This model is felt to be a good working model for Alzheimer's type pathology in humans. The ME7 treated mice were compared with non-ME7 treated mice and subjected to an intraperitoneal challenge of LPS, to mimic a peripheral mild infection, or saline. Working memory was tested using a shallow water T-maze with alternating escape routes (Murray et al., 2012). Prior to challenge the ME7 mice had increased numbers of microglial cells and a greater proportion of primed microglial cells. Post LPS challenge the mice with neurodegeneration showed an acute and transient worsening of working memory, which was also associated with a prolonged and increased production of CNS cytokines TNF $\alpha$ , IL-1 $\beta$



and IFN $\beta$ . Therefore, the model demonstrates both vulnerability to delirium, in terms of microglial priming in neurodegeneration, and central inflammation in response to a peripheral inflammatory challenge (immune to brain communication). The clinical manifestations of delirium as seen in the mice are only seen in the presence of this central inflammatory response. This animal model has also been used to demonstrate similar working memory deficits post LPS in animals with selective cholinergic neuronal loss (Field et al., 2012).

Figure 1-6 attempts to bring together the information discussed in the neuroinflammatory hypothesis of delirium, in contrast to the clinical features illustrated in Figure 1-6.



**Figure 1-6: Schematic representation of the neuro-inflammatory hypothesis of delirium**

#### 1.1.7.6 The Hypothalamic-pituitary-adrenal axis in delirium

The hypothalamic-pituitary-adrenal (HPA) axis is the major neuroendocrine axis concerned with the regulation of stress and achieves its effects via an increase in glucocorticosteroids. These regulate the inflammatory response and act through negative feedback to ameliorate the activation of the HPA axis (Aguilera, 2011). Given that delirium is primarily caused by stress, it is plausible that the HPA axis is an important mediator of delirium.

In response to stress catecholamines are released from the adrenal medulla, and cortisol and dehydroepiandrosterone (DHEA) are released from the adrenal cortex. DHEA is converted to dehydroepiandrosterone sulphate (DHEAS), which is the active form in serum. Both cortisol and DHEA/DHEAS are immune-modulating, with cortisol being broadly immune suppressive and DHEA/DHEAS being broadly immune enhancing. As we age the production of DHEA decreases, leading to an imbalance of immune suppressive and enhancing effects, so called adrenopause (Orentreich et al., 1992). The actions of cortisol and DHEAS are summarised in Table 1-4 (Phillips et al., 2007)

**Table 1-4: Effects of cortisol and DHEAS on immune function and inflammation. Adapted from Phillips et al 2007**

Cortisol	DHEAS
Inhibits neutrophil function	Improves neutrophil function
Reduces extravasation of inflammatory cells	Improves NK cell cytotoxicity
Decreases production of pro-inflammatory cytokines, inc TNF, IL8	Increases anti-inflammatory cytokine production
Induces cell death of immune cells	Reduces cell death of immune cells

This imbalance may be a driver behind the vulnerability to delirium seen in older patients with delirium

Raised glucocorticoid levels have long been associated with the stress response and “Sickness Behaviour” (Cunningham and Maclullich, 2013) through activation of the hypothalamic-pituitary-adrenal (HPA) axis. In healthy volunteers, LPS injection causes not only a rise in inflammatory cytokines, but also cortisol. These rises are dose dependent and also cause both mood and working memory deficits (Grigoleit et al., 2011). Age related dysregulation of the HPA axis due to the adrenopause, which results in a decline in DHEA and a slight increase in serum cortisol (Orentreich et al., 1992), leads to an increased cortisol response, higher cortisol trough levels and prolonged high cortisol levels in response to activation (Aguilera, 2011). Similar changes are seen in patients with dementia (de Leon et al., 1988). In rodents, raised corticosterone (the rodent equivalent of cortisol) also appears to sensitise microglia and cause an exaggerated and prolonged response when stimulated with LPS (de Pablos et al., 2006).

In delirium, raised peripheral serum cortisol levels have been seen in hip fracture patients developing delirium (Bisschop et al., 2011, van Munster et al., 2010) and baseline raised cortisol preoperatively has been shown to predict delirium (McIntosh et al., 1985). Raised serum cortisol in those developing delirium as compared with no delirium has also been reported in septic patients (Pfister et al., 2008), and in two reports after cardiac surgery those post cardiac surgery (Mu et al., 2010, Plaschke et al., 2010). Raised cortisol has been reported in the CSF of hip fracture patients developing delirium compared to those not developing delirium (Pearson et al., 2010), suggesting there is also raised central cortisol. Dysregulation of the HPA axis, and in particular reduced negative hippocampal feedback causing raised basal cortisol levels have been implicated in delirium, and insufficient cortisol

responses during the dexamethasone suppression test have been reported in patients with delirium (Robertsson et al., 2001).

A recent study has attempted to model HPA-axis dysregulation onto a cohort of older patients undergoing elective hip and knee surgery. Participants had baseline cortisol measured pre-operatively, and postoperative delirium was recorded along with post-operative cortisol and IGF-1. Between participants who developed delirium and those that did not, there was no difference between preoperative cortisol. Both postoperative cortisol and cortisol fold rise was higher in the delirium group, indicating hyper responsiveness of the HPA axis may have a role in the development of delirium. The rise in cortisol also correlated with the rise in plasma IL-6, IL-8 and IL-10 (Cerejeira et al., 2013).

### 1.1.8 Summary

Delirium is a complex syndrome that presents primarily with impairment in attention and alertness. Although it has clear definitions in the primary nosological texts (DSM and ICD) it remains difficult to diagnose clinically. It is prevalent in community settings but is most prevalent among older hospitalised patients. Delirium is associated with adverse outcomes and it is not clear if treatment of delirium ameliorates these. The pathophysiology of delirium remains poorly understood, however it appears the key driver of delirium is aberrant inflammation. The lack of a clear unifying pathophysiological model suggests that exploring pathological difference between delirium subtype, outcome group, or cognitive group may results in a better understanding of delirium.

## 1.2 Dementia in general hospitals

Dementia, in contrast to delirium, is a syndrome of chronic progressive cognitive impairment. It presents with deficits in memory and other cognitive domains, and these impact on a person's daily life and function. Dementia affects about 36 million people worldwide, with numbers expected to double over 20 years to 66 million by 2030 (Alzheimer's Disease International, 2009). In the United Kingdom, dementia affects 850,000 people, with a prevalence of 7.1% in people older than 65 years. This is forecast to rise to 1 million by 2025 and to over 2 million by 2051 (Alzheimer's Society, 2014). The prevalence of dementia rises with age, with a prevalence of 12.2% in the 80-84 year age group and 32.5% in those over 95 years old. Prevalence data for the United Kingdom was derived by the Delphi method using six studies on late onset dementia. The estimated prevalence across age groups along with the source prevalence data is presented in Table 1-5. The cost of dementia to the UK is reported to be £26.3 billion, with an average cost of £32,250 per person per year with dementia.

Although the estimated prevalence of dementia is predicted to rise, estimates of increasing prevalence have been challenged by findings from the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS) (Matthews et al., 2013). This was a cohort study of randomly sampled older people over 65 years and was based in the community in three distinct geographical areas of the UK. They reported no increase in prevalence across two separate time points. The first data was collected between 1989 and 1994 (CFASI), and measures repeated between 2008 and 2011 (CFASII). The adjusted prevalence of dementia in people over 65 years in CFASI was 8.3% and in CFASII was 6.5%. This represents an actual fall in prevalence over time in the cohort. It has been suggested this may be due to better

primary prevention of conditions associated with risk factors for dementia such as hypertension, heart disease and stroke.

**Table 1-5: The UK prevalence of dementia in age groups. The current UK consensus is presented with other important cohort estimates. Adapted from Dementia UK, Alzheimer's Society, 2014.**

Age in years	65-69	70-74	75-79	80-84	85-89	90-94	95+
<i>Consensus estimates</i>							
Current UK consensus	1.3	2.9	5.9	12.2	20.3	28.6	32.5
ADI/Lancet consensus (Ferri et al., 2005)	1.5	3.6	6.0	12.2	24.8		
Alzheimer's Society estimates (Alzheimer's Society, 2014)	2.0	5.0		20.0			
<i>Estimates from key surveys</i>							
EURODEM meta-analysis (Launer et al., 1999)	1.4	4.1	5.7	12	21.6	32.2	34.7
MRC CFAS (Matthews et al., 2013)	1.5	2.6	6.3	12	25.3		

### 1.2.1 Definitions of Dementia

Dementia is defined in both the Diagnostic and Statistical Manual of Mental Disorders and the International Classification of Disease. They state core criteria required to make a general diagnosis of dementia and specific criteria required to diagnose both dementia and the sub-type of dementia. It is beyond the scope of this thesis to discuss in detail all the classifications of dementia but a brief summary, specific to Alzheimer's disease and Vascular dementia will be given.

The DSM-IV defines the essential feature of dementia as the development of multiple cognitive deficits that are sufficiently severe to cause impairment in occupational or social functioning. Cognitive deficits are memory impairment, with impairment in at least one other cognitive domain. Memory impairment is described as the inability to learn new information as well as forgetting previously learned information. Four other cognitive domains are described in DSM-IV. These are 1) aphasia (language disturbance, either comprehension or expression, both written and spoken), 2) apraxia (difficulty in executing motor tasks such as walking, dressing, combing hair), 3) agnosia (difficulty in recognising and identifying objects or family members), and 4) executive functioning (difficulty in planning and executing complex thinking or tasks, such as work, budgets, activities). The cognitive deficits must be a decline from baseline. Importantly the cognitive deficits must cause a significant impact on a person's functioning. Examples given in the DSM-IV are impairments in working, shopping, dressing, bathing and handling finances. However, dementia cannot be diagnosed if these symptoms occur in the course of delirium, or are better explained by another psychiatric or neurological disorder.

Once the core features of dementia have been met, then subtype can be described. Dementia of the Alzheimer's type requires the above core criteria as well as a disease course characterized by gradual onset and continuing cognitive decline. Vascular dementia requires the above criteria and evidence of focal neurological signs or symptoms, or laboratory evidence of cerebrovascular disease.

Similar to the DSM-IV, dementia in the ICD-10 requires evidence of decline in memory and thinking sufficient to impair personal activities of daily living. This must be in the presence of clear consciousness (i.e not 'clouded' consciousness as in the ICD definition of delirium) and

has to be evident for at least six months. The decline must be in the absence of clinical evidence or special investigations that suggest the decline is due to a systemic or brain disease other than dementia.

The ICD-10 subtype definitions include vascular dementia, which requires the above criteria as well as a history of uneven impairment and progression with preceding focal neurological events (Transient ischaemic attack, brief loss of consciousness). Dementia in Alzheimer's disease requires that the onset is insidious with slow deterioration and there are no features of vascular dementia early in the disease course.

The key difference between the two criteria is that the ICD-10 specifies that symptoms must have been present for a minimum of six months as well as a suggestion that investigation such as computer tomography scanning (CT scan) of the brain is necessary.

There is a further classification of Alzheimer's disease, known as the NINCDS-ADRDA criteria (McKhann et al., 1984). This breaks the diagnosis down into probable, possible, and definite Alzheimer's disease. They require a specific set of investigation to be completed as well as neuropsychological testing.

Mild cognitive impairment (MCI) is a syndrome of reported memory loss and measurable cognitive deficit, but the deficit is not severe enough to affect activities of daily living. It is associated with a 5-10% yearly risk of development into dementia with 21.2 to 39.2% eventually developing dementia (Mitchell and Shiri-Feshki, 2009). MCI is defined by the current consensus definition (Winblad et al., 2004): (1) the person is neither normal nor demented, (2) there is evidence of cognitive decline, and (3) that activities of daily living are preserved and complex instrumental functions are either intact or minimally impaired.



This thesis will use the DSM-IV criteria when describing and diagnosing dementia.

#### 1.2.1.1 Dementia recognition

The diagnosis rate of dementia is calculated by using estimates of dementia prevalence and figures of recorded dementia diagnosis. In the United Kingdom the estimated diagnosis rate in 2013 was 48.7%, an increase from 37% in 2007 (Department of Health, 2013). Improving diagnosis rates is a key aspect of the World Alzheimer's Report of 2011 (Alzheimer Disease International, 2011) and the UK National Dementia Strategy (Burns and Robert, 2009). Cohort studies of older people that are not selected based on cognitive function can offer an insight into the factors influencing diagnosis rates. A cohort study with a final study sample of 856 people (The Aging, Demographics and Memory Study, ADAMS) was derived from a large longitudinal study of ageing from the United States, the Health and Retirement Study. 307/856 (35%) were given a diagnosis of dementia using DSM-IV criteria and the participants and informants were asked if the diagnosis had ever been made previously by a health professional. Only 42% (95% CI 33–51%) had a previously recognised diagnosis of dementia. Participants without a recognised diagnosis were more likely to be male, older, unmarried and in the bottom quartile of educational attainment (Savva and Arthur, 2015).

#### 1.2.2 Dementia in general hospitals

Compared to dementia seen in community settings, dementia in general hospitals demonstrates a different observed phenotype. An estimated 25% of all hospital bed days are occupied by someone with dementia (Alzheimer's Society, 2009b) and an estimated 6% of people with dementia are inpatients in acute hospitals at any given time-point. Dementia in general medical patients is common, unrecognised, relatively severe and associated with both in-hospital adverse events and adverse outcomes. This specific observed phenotype of

medical inpatients with dementia and cognitive impairment has been described in detail by two recent well-conducted cohort studies. A systematic review published prior to these studies also offers an insight into this observed phenotype. These are described in Table 1-6 and the following descriptions of dementia in general hospital will be mainly based on these. They will be described as the North London cohort and the Nottingham cohort throughout the text

**Table 1-6: Characteristics and key finding from two major cohorts describing dementia and cognitive impairment in general hospital**

Study	Population	Prevalence	Severity	In hospital associations	Outcome
Systematic review (Mukadam and Sampson, 2011)	14 studies >55 years General hospital medical and surgical inpatients Excluding hip fracture patients	2.8% - 63% (14 studies) 25.1%-43.3% (3 studies using DSM-IV criteria)	Not described	Patients with dementia were older, female and from a NH (6 studies)	Increased length of stay (3 studies) Institutionalisation (2 studies) increased delirium (1 study)
North London cohort  (Sampson et al., 2009, Watkin et al., 2012, Sampson et al., 2013, Sampson et al., 2014)	>70 years old Unplanned acute admissions or medical unit Excluding surgical admissions N=617 83.0 yrs., 59% female	42% with DSM-IV dementia 21.1% recognised diagnosis	46% FAST stage of >6d 75% BPSD 45% with mod/severe BPSD	Dementia has 2.18 RR of adverse event in hospital More likely to be admitted from care home More likely to have pressure sores	HR 2.09 for death during index admission 12 month outcomes: median survival 1.1 yrs. vs 2.7 years in those with dementia HR 1.66 for mortality (unadjusted)
Nottingham cohort  (Goldberg et al., 2012, Bradshaw et al., 2013, Glover et al., 2014)	>70 years old General medical and trauma orthopaedics admissions Excluding surgical specialities 1,004 screened N=250, 84.0 yrs, 66% female	50% with cognitive impairment Half with a recognised diagnosis	14% with delusions 20% with hallucinations 17% with agitation/aggression 38% with apathy	Cognitive impairment associated with being older, from a care home, with increased incontinence and greater functional dependence	180 day outcomes: 31% died, 42% readmitted, 31% survived without being readmitted or moving to a care home

#### 1.2.2.1 Prevalence and presentation

Dementia is common among older people in hospitals. A meta-analysis in 2011 identified 14 studies that reported the prevalence of dementia in hospitals ranging from 2.8% to 63%. In three studies, using the most recent DSM-IV criteria prevalence ranged from 26.1% to 43.3%. The main difficulty in describing accurately the prevalence of dementia in this cohort is distinguishing between delirium and dementia. This will be described in more detail in later sections. Only five of the 14 studies reporting dementia prevalence in hospitals screened for and excluded delirium (Mukadam and Sampson, 2011).

In the North London cohort consecutive medical admissions of people over 70 years old were assessed for both delirium and dementia, with dementia being diagnosed using DSM-IV criteria. Dementia diagnosis was made following assessment by a specialist old age psychiatry doctor using an algorithm based on the DSM-IV criteria. Delirium was screened for using the confusion assessment methods (CAM) and those with delirium initially excluded. If the delirium recovered in the study period they were then included. They report a prevalence of 42.2% in 610 participants assessed (Sampson et al., 2009).

In the Nottingham cohort the prevalence of cognitive impairment (defined by abnormal Mini-Mental State Examination) is estimated to be 50% among people over 70 admitted to general hospital. They were unable to separate dementia per se from other causes of cognitive impairment. Depression and delirium was screened for, and it is reasonable to conclude that this reported cohort included dementia and mild cognitive impairment (Goldberg et al., 2012).

Dementia and cognitive impairment presents to hospital in a varied fashion. It typically presents ‘in crisis’. This is where another medical crisis, such as functional decline, falls, or delirium, leads to the unmasking of a previously unrecognised dementia. The Nottingham cohort recorded 7 different geriatrician assessed functional problems and 23 different geriatrician assessed admission diagnoses in 53 older people with cognitive impairment (Glover et al., 2014)(Table 1-7)

Although dementia affects almost half of older people admitted to general hospitals (Sampson et al., 2009) (Goldberg et al., 2012), strikingly only half of these people have a formal diagnosis of dementia prior to admission. The North London cohort reports that in only 49% of those with dementia, was this known prior to index admission. The Nottingham cohort report similar findings with only 50% of those with cognitive impairment having a recorded history of dementia. Extrapolating these figures, a typical 500-bedded general hospital has at least 50 patients with undiagnosed dementia (Russ et al., 2012).

Patients with dementia in general hospital tend to be older than non – demented hospital patients. A pooled estimate of this is that they are significantly older by four to seven years (Mukadam and Sampson, 2011). They are more likely to be women, and more likely to come from a nursing home.

**Table 1-7: Diagnoses recorded of older patients admitted with cognitive impairment to general hospital. Adapted from Glover 2014**

Most common ICD10 coded diagnoses	Most common geriatrician assessed presenting functional problem	Most common geriatrician assessed diagnosis	
Fractured neck of femur	Immobility 38 (73%)	Fractured neck of femur 7	Painful hip post fall 2
UTI	Falls 34 (64%)	Other fractures 6	Unexplained delirium 2
‘senility’	Pain 28 (54%)	Pneumonia 4	Cancer 2
Pneumonia	Incontinence (46%) 24	Multifactorial fall 4	Exacerbation of COPD 1
Heart Failure	Breathlessness (23%) 12	Multifactorial functional problem 3	Infected leg ulcer 1
COPD	Increased confusion 11 (21%)	Atrial fibrillation with fast ventricular response 3	Gastroenteritis 1
	Dehydration (21%) 11	Dehydration/renal failure 3	Stroke 1
		UTI 1	Ruptured Achilles tendon 1
		Alcohol intoxication 2	Rheumatoid arthritis 1
		Adverse drug reaction 2	Progression of vascular dementia 1
		Seizures 2	Acute urinary retention 1
		Unresponsive episode 2	Anxiety 1

#### 1.2.2.2 Dementia in general hospital is relatively severe

People with dementia in hospital have more severe disease. Recent analysis from the North London cohort reports high levels of functional impairment and behavioural and psychiatric symptoms. 46% had a Functional Assessment Staging Scale (FAST) stage of 6d or above.

This scale describes a continuum of seven progressive stages of dementia. A patient at 6d or above would be incontinent and only able to speak a few words, if any. They may also be immobile. Three quarters of the patients with dementia had behavioural and psychological symptoms of dementia (BPSD), and 43% had symptoms that caused trouble for the staff involved. These rates are much higher than would be expected in a general population of dementia in community settings. Patients with dementia in hospital also have low reported quality of life (Sheehan et al., 2012). There is also a high rate of undiagnosed pain in dementia patients in hospital that may contribute to behavioural symptoms (Sampson et al., 2015).

#### 1.2.2.3 Dementia in general hospital is associated with adverse outcomes.

Dementia in general hospitals is associated with an increased rate of adverse events while in hospital (Mecocci et al., 2005). Patients with dementia have an increased risk of falls (OR 1.6), pressure sores (OR 4.9), faecal incontinence (OR 6.3) and urinary incontinence (OR 5.3) as well as higher rates of mortality and higher length of hospital stay (Sampson et al., 2013). The reason for this is not clear, but the hospital care of people with dementia is often the focus of complaints and scandals involving poor care. It was a feature of the recent Francis report into failings of care at Mid Staffordshire Hospital. An influential report by the Alzheimer's Society (Alzheimer's Society, 2009a) reported that hospital staff often struggle to meet the complex care needs of patients with dementia and lack training. There is also a perception that patients with dementia are in the wrong place, often leading to negative care (Tadd et al., 2011)

People with dementia have worse health outcomes than similar people in hospital without dementia. The median survival time from admission of the North London cohort was 1.1

years in those with dementia, and 2.7 in those without. Nearly half of those with dementia had died at 12 months. They report a hazard ratio, adjusted for comorbidity, age, and illness severity, of 1.24 (95% CI 0.95–1.60) (Sampson et al., 2013). In a cohort of older patients with dementia referred to a liaison psychiatry service while in hospital, mortality was 31% at six months and 40% at 12 months (Sheehan et al., 2013). They report a large increase in care home residence at 12 months. 13% of the cohort were in a care home pre-admission, and 84% were in a care home at 12 months, suggesting a significant risk of new institutionalisation as a result of hospital admission. The Nottingham cohort report six-month outcomes of people with cognitive impairment. At six months 31% had died, 24% had moved to a new care home and 42% had been readmitted to hospital. Of the whole cohort, only 31% were still alive, living in their own home and had not been readmitted (Bradshaw et al., 2013). A further study reports 200 consecutive medical admissions screened for cognitive impairment using the Mini-Mental State examination and the Clock Drawing Test (Torisson et al., 2012). A single abnormal test was associated with a hazard ratio of 2.86 (1.28-6.39) for mortality over a 12-month follow-up. An abnormality on both tests (39% of people screened) was associated with a HR of 3.39 (1.54-7.45)



## 1.3 The relationship between delirium and dementia

Dementia is the greatest risk factor for developing delirium in hospital. Delirium superimposed on dementia (DSD) accounts for up to 65% of all older people with delirium in hospital (Fick et al., 2002). Delirium can worsen already existing dementia (Fong et al., 2009a) and is an independent risk factor for novel incident dementia (Davis et al., 2012). Dementia complicates both the classification and diagnosis of delirium as well as making research in older delirium populations more difficult. In the context of the acute general hospital dementia and delirium are intricately linked. Indeed, it is difficult to talk about one without the other. The next section will describe the relationship between delirium and dementia in more detail.

### 1.3.1 Delirium superimposed on dementia (DSD)

Clinically the most difficult diagnostic problem in an older person presenting with confusion is to disentangle delirium from dementia. The possibilities are either they have delirium, or dementia, or they have delirium superimposed on a pre-existing dementia. This is made more difficult as a proportion of people will have dementia that is not recognised, as well as the possibility of a persisting delirium. Delirium in people with dementia is therefore more likely to go unrecognised (Fick et al., 2002). The DSM-IV criteria for delirium and dementia both state that it is not possible to make the diagnosis of one condition in the presence of the other. However, in the DSM-IV criteria for both dementia of the Alzheimer's type and vascular dementia, there is a code for the diagnosis of delirium superimposed on the dementia - 'with delirium' (codes 290.3 and 290.41). Conversely in the ICD-10 definition of delirium, there is a separate code (F05.1) for delirium that develops in the course of dementia.

#### 1.3.1.1 Diagnosing delirium in people with dementia (DSD)

People with dementia have by definition a chronic cognitive decline. They may also have some of the features typically seen in delirium, such as attentional deficit. Arousal and alertness are usually preserved in dementia however. Thus diagnosing delirium in a person with dementia is more challenging than in someone with no baseline cognitive deficit. It is worth examining how common diagnostic tools for delirium perform when used in people with dementia. Both the confusion assessment method (CAM) and the 4AT test have been examined in this context. A systematic review of tools to detect DSD (Morandi et al., 2012) reported a single study of the CAM in the context of diagnosing DSD. This demonstrated the CAM had a higher sensitivity (96–100% i.e. greater true positives) at the expense of lower specificity (77% i.e. higher false negatives). The validation study of the 4AT included 30% of people with dementia, and 23% with DSD. Similarly the sensitivity improved (89.7%% to 94%) with loss of specificity (84.1% to 65%). Given the cognitive deficits in both conditions, this is not surprising as it would be expected that people with dementia might also test positive for delirium.

There are two core diagnostic challenges when making a diagnosis of DSD. Dementia with Lewy Bodies (DLB) is a form of dementia affecting 4.2% of all dementia in the community (Vann Jones and O'Brien, 2014). DLB typically presents with a more rapid onset than other dementias and presents with fluctuating degrees of cognitive impairments, attentional deficits and hallucinations. As such, in clinical practice, delirium can often present in a similar way to DLB, especially persisting delirium. A further diagnostic challenge is that of behavioural and psychiatric symptoms (BPSD) in dementia (Kales et al., 2015) which are present in up to 75% of people with dementia in hospital (Sampson et al., 2014). These can typically include altered arousal (especially increased arousal), hallucinations and agitation. BPSD can

sometimes be misdiagnosed as delirium and vigilance is needed to ensure the diagnosis of delirium is correct in both these situations.

#### 1.3.1.2 Diagnosing dementia in people with delirium

By definition, people with delirium have cognitive deficits that are acute and fluctuating in course. In this context traditional performance based tools to detect dementia and measure cognitive deficits are not valid. Information about baseline pre-morbid cognition can be gathered however at admission to hospital from an informant. This may then allow a diagnosis of dementia to be made. However to date there has been no published systematic way of achieving this. It would seem possible that traditional performance based assessments of dementia could be carried out on recovery from delirium. However, a further challenge is in defining recovery from delirium. Delirium can persist and it is not clear at what stage of recovery from delirium performance based assessment become valid.

### 1.3.2 Delirium as a herald or trigger of dementia

#### 1.3.2.1 Delirium as a herald

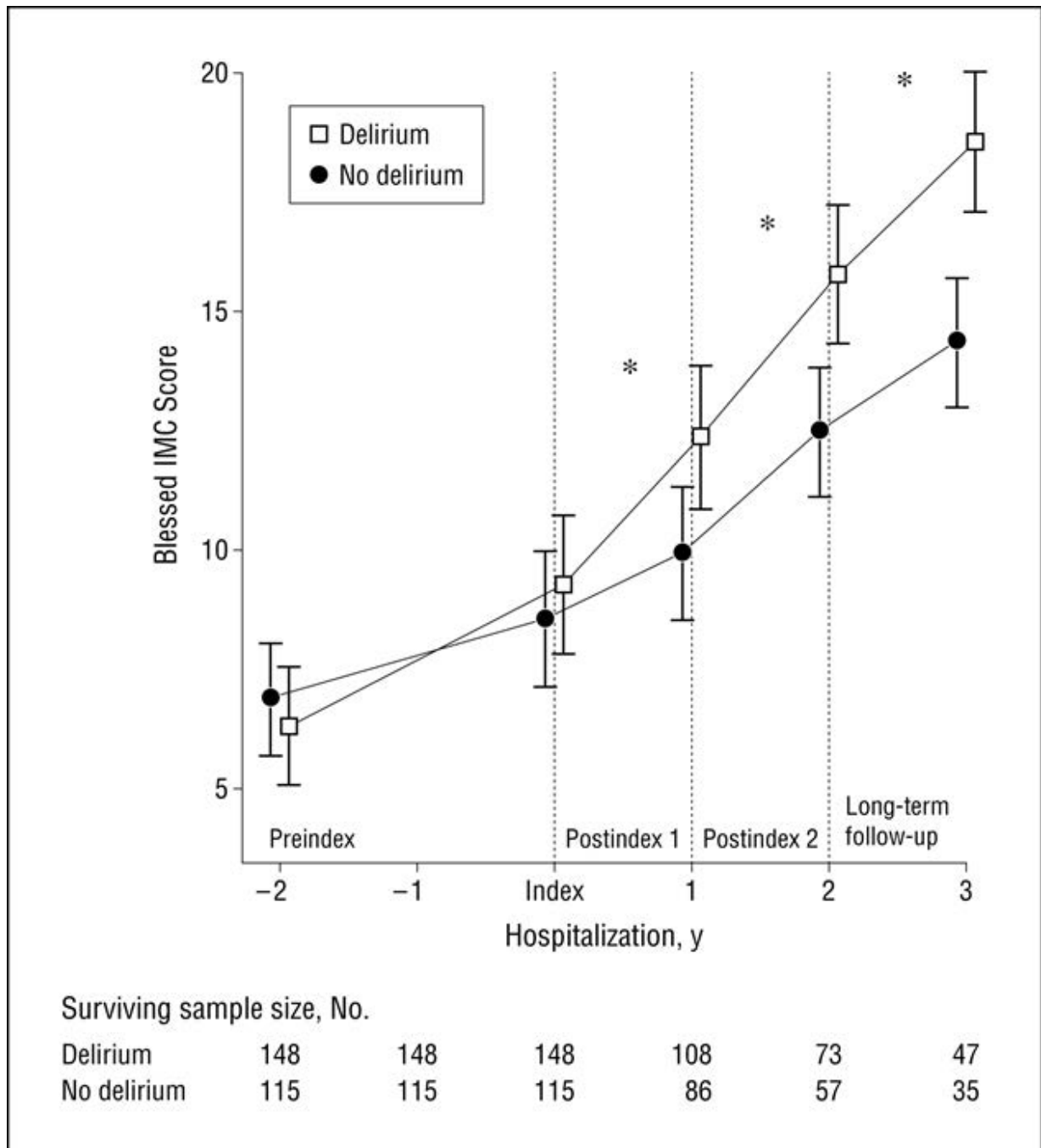
The first risk factor model for delirium development included cognitive impairment as one of four major risk factors. A systematic review found six of seven studies identified demonstrated dementia as a risk factor for delirium. However, in all of these dementia was defined by either Mini-Mental State Examination (MMSE) scores (6/7) or the Informant Questionnaire of Cognitive Decline in the Elderly (IQCODE), and not recognised reference criteria. Multivariate analysis was performed in three studies and it was possible to pool these. An OR of 6.62 (95% CI 4.30-10.19,  $p < 0.001$ ) is reported as the risk of developing delirium in people with dementia (Ahmed et al., 2014). Cognitive impairment is one of the four risk factors identified in the NICE delirium guidelines for delirium. The relationship

between dementia and delirium would also appear to be influenced by the severity of dementia. A prospective cohort of 139 older people with dementia reported a 50% increased risk of incident delirium with every increase in dementia severity score (Global Deterioration Scale, scores rated from 1-7, with increasing scores due to more severe dementia symptoms) (Fick 2013).

#### 1.3.2.2 The effect of delirium on people with dementia

A number of studies have been derived using the Massachusetts Alzheimer's Disease Research Centre cohort of older patients with Alzheimer's dementia. This cohort has regular (six monthly) clinic reviews with measurement of cognitive function, so it is possible to know cognition and cognitive trajectories before and after an episode of delirium. Cognition was measured using the Information-Memory-Concentration (IMC) section of the Blessed Dementia Scale. This scale measures from 0-37, with lower scores suggesting worse cognition. An initial study looked at cognitive trajectories across 3 years in clinic patients. If the patients were hospitalised over the study period, their notes were examined and a diagnosis of delirium made by a chart review. Comparing 336 patients without delirium to 72 with delirium, the delirium group showed a greater rate of cognitive decline post delirium episode. The mean change in IMC score was 5.4 in the delirium group and 3.1 in the non-delirium group, with difference in the rates of change as described by the slope (Fong et al., 2009a).

A sub-cohort of 263 participants who were hospitalised was derived and followed up for 3 years post hospitalisation. Delirium occurred in 56% of admissions and cognitive deterioration was greater in those with delirium (-3.1 vs -1 points per year) (Gross 2012). Figure 1-7 illustrates this decline.



**Figure 1-7: Estimated cognitive function among 263 hospitalized patients with dementia who developed delirium or did not develop delirium, showing model-implied trajectories with 95% CIs of cognitive performance at discrete time points from a random-effects regression model of the Blessed Dementia Rating Scale information-memory-concentration section (Blessed IMC) score during Massachusetts Alzheimer Disease Research Center follow-up periods. From Gross 2012**

Delirium also worsens outcomes in people with dementia in hospital. From the cohort of 771 participants with Alzheimer's disease 367 (48%) were hospitalized over the 15-year period of the study, 194 (25%) of those developed delirium. Comparing those hospitalised with delirium, those hospitalised without delirium, and those never hospitalised, the delirium group had higher mortality and new institutionalisation. The adjusted relative risk of death was 4.7 (95%CI 1.9-11.6) in the hospitalised without delirium group, compared to 5.4 (2.3-12.5) in the hospitalised with delirium group. The adjusted relative risk of new institutionalisation in the no delirium group was 6.9 (4.0-11.7) compared to 9.3 (5.5-15.7) in the delirium group (Fong et al., 2012)

Taken together, this evidence suggests that delirium worsens rates of expected cognitive decline in people with pre-existing brain disease.

#### 1.3.2.3 Delirium and future risk of dementia

Given that delirium appears to worsen dementia in pre-existing disease it would follow an episode of delirium may be associated with new incident dementia in people with no previous dementia. Two narrative reviews ((Jackson et al., 2004, MacLulich et al., 2009) report 18 studies published between 1989 and 2008 reporting on cognitive impairment after delirium. Of the 18 studies 16 report adverse cognitive outcomes after delirium. A meta-analysis in 2010 reported 6 studies, that met the authors inclusion criteria and were assessed at low risk of bias, that examined the risk of developing incident dementia after an episode of delirium in patients with no previous diagnosis of dementia. 241 participants were identified from two studies and included in meta-analysis. 56 participants developed delirium and 35 had an increased risk of dementia, whereas 15 of 185 controls had an increased risk. The two studies reported follow-up at 3.2 and 5.0 years. They report an OR of 12.52 (95% CI, 1.86-84.21) of

developing new dementia over an average follow-up of 4.1 years. Since the meta-analysis was published, two further studies have reported an increase in dementia risk in patients with delirium. 106 older patients with hip fracture, and without dementia, were recruited and followed up for 6 months. 29 (27%) developed delirium, of whom 11/29 were diagnosed with dementia at 6 months, compared to only 5/77 in the non-delirium group. They report an adjusted OR of 10.5 (95% CI 1.6-70.3) (Krogseth 2011). A cohort of 263 acute stroke patients, in whom 19% had delirium were followed up at 3 months where a diagnosis was made of post-stroke dementia. Of 213 without delirium, dementia was diagnosed in 36 (16.9%) and in 50 participants with delirium, 25 (50%) had dementia diagnosed. They report an adjusted OR of 2.65 (95% CI 1.17–6.02) that an episode of delirium causes dementia at 3 months (Meklas 2012).

These studies provide evidence that delirium is a risk factor for the development of dementia. However, all these studies have difficulties with robustly excluding pre-existing dementia, especially as the rate of formal diagnosis of dementia is about 50%. Some of the studies use the term dementia, while others cognitive impairment, for the main outcome leading to some doubt about what the true outcome is. The follow-ups are varied, and no studies were explicit about the exclusion of persistent delirium, so this may have confounded the results.

An attempt to ameliorate this problem has been seen in two recent epidemiological cohort studies aiming to ascertain whether delirium increase the risk of incident delirium. The first study, based in Finland, followed 553 people aged 85 years or older at baseline, for 10 years. At baseline, 339 were dementia free and follow-up at three, five, eight and 10 years ascertained incident dementia using DSM-III-R criteria by two neurologists. At each follow-up an episode of delirium was recorded using a retrospective history against a checklist from

the DSM-III-R criteria. These were corroborated against medical notes also available. They report that a history of delirium at any of the follow-up interviews in participants with no previous dementia was associated with an eight fold higher risk of new dementia at the next follow-up interview (OR 8.7, 95% CI 2.1–35). In keeping with previous reports they also report an acceleration in cognitive decline, as measured by decline in MMSE score, in those with delirium (Davis et al., 2012)

A further cohort study, the Cognitive Function and Ageing study (CFAS), followed 2197 participants with baseline cognitive measures for 2 years (Davis et al., 2014). Cognition was measured using a validated symptom tool that allowed an algorithmic diagnosis of both dementia and delirium. 511/2197 had dementia at baseline, and an episode of delirium in the intervening period was associated with an eight-fold increase in the risk of dementia at 2 years (OR 8.82, 95% CI 2.76 to 28.2). This study has the clear strength of being a larger population based cohort and cognition was measured serially over the 2-year period. However, as with the Vantaa 85+ study, the delirium ascertainment was retrospective and not validated against reference criteria.

So to conclude delirium might be a herald, announcing that dementia may shortly follow. However, given the close association between the two conditions and the clear increase in risk of dementia after delirium, there is a strong suggestion of a causal link.



## 1.4 Research questions and aims of the thesis

This chapter has described delirium in older people in detail, including the current understanding of delirium pathophysiology and the prediction of outcome of delirium. It has also described in detail the phenotype of dementia as observed in the general hospital setting and how this interacts with delirium.

Given this, improving the recognition and ongoing management of both delirium and dementia in general hospitals is vital. The two conditions commonly co-exist and this leads to difficulties in the practicalities. Traditionally the conditions have been researched, classified and managed separately, however it would seem almost impossible to talk about dementia in general hospitals without talking about delirium. Delirium is a high-risk condition for unrecognised dementia, but the identification of dementia in people with delirium is usually seen as too problematic to approach. **Therefore, the first research question to be addressed in the thesis is; what is the prevalence of combined cognitive impairment (dementia and mild cognitive impairment) in older people with delirium?**

The acute cognitive change and altered arousal seen in delirium makes traditional performance based tools to identify delirium not valid. As some delirium persists, it is also not clear at what stage after delirium recovery they are of use again. The systematic review has highlighted a dearth of available tools to detect dementia in general hospitals, and none in the context of people with delirium. Therefore it is clear that novel methods for identifying dementia in older people with delirium are needed. **The second research question then is; what is the validity and accuracy of informant tools to detect dementia in older people with delirium?**

The outcomes from delirium are poor. However, it is not clear who with delirium is at higher risk of these outcomes. A systematic review highlighting factors associated with adverse outcome would be useful and will form the initial element of the next research question. A structured approach that allows clinicians to predict outcomes, such as death and new institutionalisation, would afford clinicians useful information to help highlight people at risk and prognosticate. Valuable insights into the pathophysiology of delirium may also be gained by exploring differences in inflammatory profiles of those who recover well and those with adverse outcomes. **Therefore, the final research question is; among older people with delirium and dementia in a general hospital, which clinical and biochemical features are associated with adverse outcomes?**

Returning to the case study, Mrs TJ was admitted with hypoactive delirium. There are some concerns raised by her family about her pre-existing cognitive function, however at present there are no accurate tools to allow for accurate identification of a previous dementia or MCI. Although her prognosis is worse because she has delirium, as opposed to someone with the same medical precipitants but no delirium, it is not clear if she is at high risk of poor recovery. Both these important questions, if answered, would add to her medical care.

### **Thesis aims**

In a representative sample of older people admitted to hospital with delirium, the aim is to assess pragmatic methods for identification of dementia and follow-up of delirium outcomes by determining the following:

- (1) If there is dementia using DSM-IV criteria, and mild cognitive impairment, and whether this has been previously diagnosed;

(2) If a set of pragmatic tools can identify which patients with delirium are likely to have dementia;

(3) If (a) key clinical factors (duration of delirium, severity of delirium, delirium subtype), (b) routine clinical blood tests, (c) biomarkers of inflammation (IL-1 $\beta$ , IL-1ra, IL-6, IL-8, IL-10 and TNF $\alpha$ ), (d) altered steroid hormones (cortisol, DHEAS and their ratio), are associated with adverse outcomes; increased length of stay, new institutionalisation, and death.

## 2 Materials and Methods

To answer the core questions the following chapter will describe the key materials and methods used in the clinical study including; the recruitment process of a cohort of older patients with delirium and their informants, the procedures used to follow participants through to three months, laboratory methods and procedures, and finally the method used to derive a sample size. All participant-derived measures were compiled by the author who is a trained specialist in the assessment of cognition in older people.

### 2.1 Patients

Key to the project is the recruitment of a representative sample of older patients admitted to general hospital with delirium. The sample needs to be as generalizable as possible and the diagnosis of delirium accurate. Participants were recruited to form a prospective cohort of newly admitted medical patients aged over 70 years with delirium.

#### 2.1.1 Screening and identification of delirium

Patients that were admitted over the previous 24 hours to the Clinical Decisions Unit (CDU) of [REDACTED] aged 70 years and over were identified through an electronic handover system. This information was received at 8am every morning. At 9am patients not discharged, or transferred to another ward, and still on the CDU were identified, and these formed a group of potential participants. Potential participants were then screened for the presence or absence of delirium by the author. If it was not possible to screen a potential participant, the reason for this was recorded.

Potential participants were eligible for the study if they met the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV-TR) criteria for delirium (American Psychiatric Association, 2000). The robust diagnosis of delirium in participants is key to recruitment of participants. The Diagnostic and Statistical Manual of Mental Disorders (DSM) is considered the gold standard criteria for diagnosis of delirium. However to be able to inform the various criteria in the DSM, and therefore reach a diagnosis, a number of screening steps were taken.

Several screening aids were used: the Abbreviated Mental Test Score (AMTS) (Hodkinson, 1972), Digit Span test, a detailed review of the medical notes, a collateral history taken from an informant, and finally the Confusion Assessment Method (CAM) (Inouye et al., 1990).

#### 2.1.1.1 Abbreviated Mental Test Score

The Abbreviated Mental Test Score (AMTS) is a brief cognitive test commonly used in hospital as a screen for cognitive impairment (Hodkinson, 1972). As discussed in Chapter 4 in detail it is the most widely validated cognitive test in general hospital settings (Jackson et al., 2013). This was administered first in the screening process and takes 2-3 minutes to complete.

#### 2.1.1.2 Digit Span Test

The digit span forward (DSF) and digit span backwards (DSB) test was conducted as a measure of global cognition and particularly of attention. The test is based on the working memory section of the Wechsler Adult Intelligence Scale (Wilde et al., 2004). DSF and DSB were first described in use as a test for delirium in 1996 (Christensen et al., 1996) and have since been validated as a screen to detect DSM delirium in two cohorts of older medical inpatients (O'Keeffe and Gosney, 1997, Leung et al., 2011). The DSF and DSB is a non-

visual version of the spatial span test that has also been validated to detect delirium (O'Regan et al., 2014).

During the digit span test a participant is read a series of numbers, beginning with three numbers and increasing to seven, and asked to repeat them back. The numbers are first read out forward (DSF), at one second intervals. The test is then repeated; this time the participant is asked to repeat the numbers back in reverse order (DSB). The test takes 2-3 minutes to complete. If a participant was unable to repeat five numbers forward or three numbers in reverse this was considered a sign of inattention in delirium. Although no formal cut offs have been recommended in the literature, this cut off was considered the best by delirium specialists at the European Delirium Association Meeting in 2014.

Both the AMTS and DSF/DSB were chosen as they are quickly administered and appear acceptable to older people in hospital. They do not require any equipment such as a pen and paper, so can be used in people with impaired vision.

#### 2.1.1.3 Note review

The admission medical notes were reviewed to examine for corroborating history of delirium. In particular, commonly used euphemisms for delirium were examined for in the admission clerking text. These included 'confused', 'drowsy', 'acute confusional state' and 'acute or chronic confusion'

#### 2.1.1.4 Informant history

If the above screening suggested a diagnosis of delirium then a family member, or documented next of kin, was contacted. This was to ascertain baseline cognitive function, and

whether any acute change, or change from baseline in cognition, had been observed. Other elements of the history leading up to the admission were also discussed.

#### 2.1.1.5 Confusion Assessment Method

The Confusion Assessment Method (CAM) was first described in 1990 and has since become the most used and best validated detection tool for delirium (Inouye et al., 1990, Wei et al., 2008). It was developed as an operationalisation of the nine DSM-III-R criteria for delirium and was first validated over two sites in the USA (Inouye et al., 1990). Using the validation of the nine criteria, an algorithm to detect delirium was developed using the four criteria with the highest likelihood ratios. The four criteria are: 1) acute onset and fluctuation of symptoms, 2) inattention 3) disorganised thinking and 4) altered consciousness. If a test subject has features 1) and 2), with either feature 3) or 4) they have delirium.

The CAM requires a cognitive test to be done at the same time to act as a substrate for the required information to make a diagnosis. The original validation paper used the Mini Mental State Examination (MMSE). However, due to copyright issues, as well as the need for pen and paper, the AMTS, DSF and DSB were used. The four CAM criteria are given in more detail in Table 2-1

**Table 2-1: Diagnostic criteria for delirium using the Confusion Assessment Method. From (Inouye 1990)**

Feature 1	Acute onset and fluctuating course
	This feature is usually obtained from a family member or nurse and is shown by positive responses to the following questions: is there evidence of an acute change in mental status from the patient's baseline? Does the (abnormal) behaviour fluctuate during the day, that is, tend to come and go, or increase and decrease in severity?
Feature 2	Inattention
	This feature is shown by a positive response to the following question: does the patient have difficulty focusing attention, for example, being easily distractible, or having difficulty keeping track of what was being said?
Feature 3	Disorganised thinking
	This feature is shown by a positive response to the following question: is the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?
Feature 4	Altered level of consciousness
	This feature is shown by any answer other than "alert" to the following question: Overall, how would you rate this patient's level of consciousness? (alert [normal], vigilant [hyperalert], lethargic [drowsy, easily aroused], stupor [difficult to arouse], or coma [unarousable])

The diagnosis of delirium by CAM requires the presence of features 1 and 2 and either 3 or 4

A systematic review identified 22 studies describing the diagnostic test accuracy of the CAM and a version of the CAM for use in the intensive care unit (CAM-ICU). Nine studies reported diagnostic test accuracy of the CAM where the reference test was DSM-IV. The authors report a pooled sensitivity of 82% (95% CI 69-91%) and specificity of 99% (87-110%) (Shi et al., 2013). Of note, all studies required a degree of training for the administrator to obtain accurate results. Given the relatively low sensitivity with a high specificity, there is a risk of false negative results, so the authors conclude that clinical judgement should be used, in addition to the CAM, to make an accurate diagnosis of delirium.



The AMTS, digit span tests and clinical assessment were used to inform the CAM, criteria and potential participants were recorded as CAM positive or CAM negative

### 2.1.2 DSM-IV-TR diagnosis of delirium

Using the tools described above it was then possible to make a diagnosis of delirium, using the criteria set out in DSM-IV-TR. This was the key step to ensure that participants had a diagnosis of delirium against a recognised reference standard, rather than a diagnosis made solely using a screening instrument such as CAM. All four DSM-IV-TR criteria needed to be met for the diagnosis to be made. The criteria are described in Table 2-2.

**Table 2-2: Diagnostic criteria for delirium as set out by DSM-IV-TR and used to make reference diagnosis of delirium**

Diagnostic criteria for delirium (293.0)	
A	Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain or shift attention.
B	A change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a pre-existing, established, or evolving dementia.
C	The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.
D	There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition.

### 2.1.3 Recruitment

Patients with DSM-IV-TR delirium who met the inclusion criteria and did not meet exclusion criteria were then invited to participate. To ensure the cohort was as inclusive as possible the exclusion criteria were limited. These were as follows:

Inclusion criteria: 1) Aged 70 years old and over

2) DSM-IV-TR delirium assessed within 24 hours of admission to hospital

- Exclusion criteria
- 1) Inability to communicate due to severe sensory impairment
  - 2) Non-competence in the English language
  - 3) Deemed to be at imminent risk of death

Participants with severe sensory impairment would have difficulty with completing all the assessments needed through the course of the study so it was felt reasonable to exclude those this group, as attempting the assessments may cause upset or distress. Non-competence in the English language would have made the performance-based assessments for both screening of delirium and diagnosis of dementia very difficult and not valid, as reliable and validated translations of the tools do not exist. It was anticipated that some older people with delirium would be severely ill and at the end of life. If it was felt at initial assessment that the patient was at imminent risk of dying then they were not approached to participate. It was likely that approaching both patient and family in this situation may potentially cause unnecessary distress.

#### 2.1.4 Consent

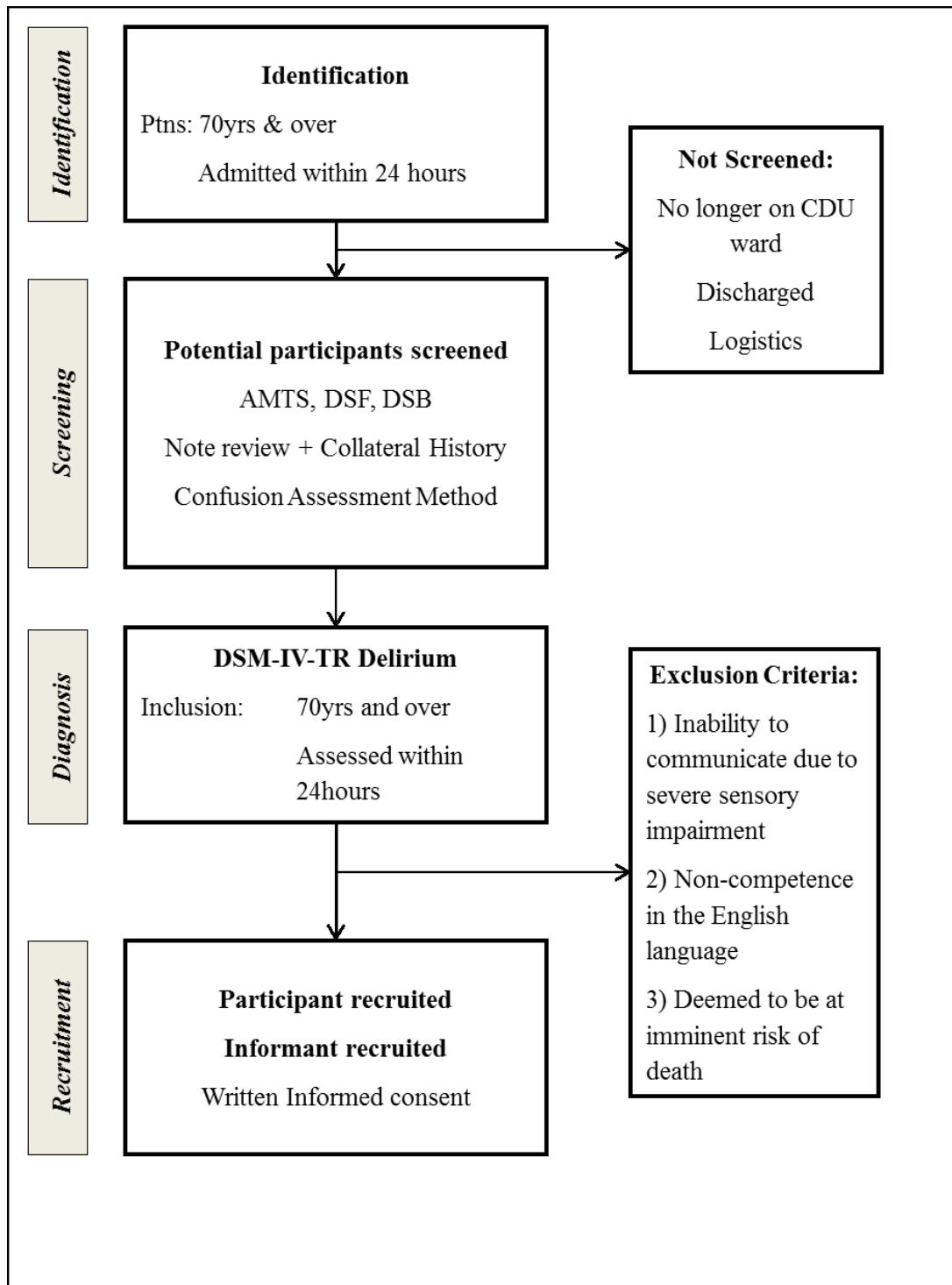
Written informed consent was sought from the potential participant if they had the mental capacity to give it. This was assessed during the screening process and complied with the principles of capacity to consent as laid out in the Mental Capacity Act 2005 (Her Majesty's Government, 2005). It was anticipated that the majority of participants would lack capacity due to the nature of delirium. For those who lacked the mental capacity to give informed

consent, the next of kin was consulted in accordance with the provisions of the Mental Capacity Act, Chapter 9, Part 1, with respect to participation in research.

Participants with no capacity to consent were monitored throughout the study at points of assessment. If they regained capacity to consent then informed consent was taken at that time.

The consultee was also approached to act as a study informant. If there was no need for a consultee then the documented next of kin was approached to act as a study informant. Written informed consent was also gained from the study informants.

The recruitment and consent process is summarised in Figure 2-1



**Figure 2-1: Flowchart of identification and recruitment of potential participants into the study**

### 2.1.5 Informant interview

An interview with the study informant was then carried out on the day of recruitment. Information regarding previous diagnosis of dementia or cognitive impairment was ascertained as well as a history regarding prior cognitive and physical function. This was measured using the Barthel scale (Collin et al., 1988) that is a scale of physical function and activities of daily living. At this point the informant was asked to complete the two informant scales, the Informant Questionnaire of Cognitive Decline in the Elderly (Jorm and Jacomb, 1989) (IQCODE) and the Washington University Dementia Screening Test - Alzheimer's disease 8 (Galvin et al., 2005) (AD8). Instructions on how to complete the scales were given to the informant, and at that point, the researcher left the room. The scales were completed in private and once completed placed in an envelope. The researcher re-entered and the interview was completed. This was to ensure the researcher was blind to the results of the IQCODE and AD8 for the remainder of the study period.

#### 2.1.5.1 The Informant Questionnaire of Cognitive Decline in the Elderly (IQCODE)

The IQCODE is a tool to screen for and diagnose dementia. Traditional methods of screening involve using a cognitive test directly with the participant, so called performance-based assessments. The IQCODE however uses information from an informant to populate the scale. It asks the informant to rate any changes over the previous 10 years in the subject's ability to perform tasks due to problems with thinking and memory. Each item is rated from 1 to 5, with 3 being no change, 1 the most improved change and 5 being the worst change. Each item is summed and an average score is given. The final score therefore ranges between 1 and 5, with 3 being a neutral score and higher scores representing worse cognitive decline. It was first published as a 26-item tool and shown to correlate with the MMSE in 64 older people across a community setting (Jorm and Korten, 1988). A subsequent larger study in

922 community participants, including 309 with recognised dementia demonstrated good inter-rater reliability (Jorm and Jacomb, 1989). A short form using the 16 most discriminating items was developed and this has become the clinical norm due to its ease of use and reduced burden (Jorm, 1994). A systematic review of studies using the IQCODE in secondary care was published in 2015. Thirteen studies reported the diagnostic test accuracy of the IQCODE to detect dementia against a recognised reference standard. Of those 13: one study reported the diagnostic test accuracy of the IQCODE to detect dementia in exclusively medical inpatients, two reported a mixed group of inpatients and outpatients, and the rest of the studies were based exclusively in the outpatient clinic setting. It was not possible to extract the diagnostic test accuracy of the in-patients only from the mixed studies. The prevalence of dementia across the studies ranged from 10.5% to 87.4%. Pooled analysis, using a cut off of  $>3.3$  as representing dementia, reports a sensitivity of 0.91 and specificity of 0.66, a positive likelihood ratio (LR+) of 2.7, and a negative likelihood ratio (LR-) of 0.14 (Harrison et al., 2015). The single study in hospital inpatients, using a cut-off of  $>3.44$ , reported a sensitivity of 1.00 and a specificity of 0.86 (Harwood et al., 1997).

Although the IQCODE-SF has not been formally assessed in people with delirium, it is commonly used as a proxy for previous cognitive impairment in delirium research using different cut offs. A cut off of  $>3.30$  has been used in studies of intensive care unit delirium (Pisani et al., 2007) and a cut off of  $>3.5$  in a general hospital population (O'Regan et al., 2014). The IQCODE-SF has also been reported to predict postoperative delirium in elective surgery patients (Priner et al., 2008). The introductory wording was changed to 'Now we want you to remember what your friend or relative was like 10 years ago and to compare it with what he/she was like *before they got the illness that brought them to hospital*'. See appendix 1.

It takes about 10 minutes for the informant to complete

		1	2	3	4	5
1	Remembering things about family and friends, eg occupations, birthdays, addresses	Much improved	A bit improved	Not much change	A bit worse	Much worse
2	Remembering things that have happened recently	Much improved	A bit improved	Not much change	A bit worse	Much worse
3	Recalling conversations a few days later	Much improved	A bit improved	Not much change	A bit worse	Much worse
4	Remembering her/his address and telephone number	Much improved	A bit improved	Not much change	A bit worse	Much worse
5	Remembering what day and month it is	Much improved	A bit improved	Not much change	A bit worse	Much worse
6	Remembering where things are usually kept	Much improved	A bit improved	Not much change	A bit worse	Much worse
7	Remembering where to find things which have been put in a different place from usual	Much improved	A bit improved	Not much change	A bit worse	Much worse
8	Knowing how to work familiar machines around the house	Much improved	A bit improved	Not much change	A bit worse	Much worse
9	Learning to use a new gadget or machine around the house	Much improved	A bit improved	Not much change	A bit worse	Much worse
10	Learning new things in general	Much improved	A bit improved	Not much change	A bit worse	Much worse
11	Following a story in a book or on TV	Much improved	A bit improved	Not much change	A bit worse	Much worse
12	Making decisions on everyday matters	Much improved	A bit improved	Not much change	A bit worse	Much worse
13	Handling money for shopping	Much improved	A bit improved	Not much change	A bit worse	Much worse
14	Handling financial matters, eg the pension, dealing with the bank	Much improved	A bit improved	Not much change	A bit worse	Much worse
15	Handling other everyday arithmetic problems, eg knowing how much food to buy, knowing how long between visits from family or friends	Much improved	A bit improved	Not much change	A bit worse	Much worse
16	Using his/her intelligence to understand what's going on and to reason things through	Much improved	A bit improved	Not much change	A bit worse	Much worse

**Figure 2-2: The IQCODE as presented to participants**

#### 2.1.5.2 AD8: The Washington University Dementia Screening Test (AD8)

The AD8 is a brief informant based tool to detect dementia. It requires the informant to indicate if there has been a change in the subject's ability to complete eight everyday tasks due to thinking and memory. They are asked to compare this over the 'last several years' and are able to respond yes, no, or don't know. The number of yes responses is summed giving a score of between 0 and 8, with higher scores indicting greater cognitive impairment. The AD8 was developed as a brief informant tool and initially validated in a memory clinic setting (Galvin et al., 2005) with further studies showing good validity and inter-rater reliability (Galvin et al., 2006). It has also been used as a self-rating item (Galvin et al., 2007a) and been associated with Alzheimer's pathology and CSF biomarkers (Galvin et al., 2010). A further report investigated the AD8 to detect dementia at a population screening level and

found it to be good at distinguishing between no dementia and mild dementia (Malmstrom et al., 2009). It has all the benefits of the IQCODE, but is shorter and can also be administered over the telephone. There are no studies in older inpatients to date, but two studies have looked at the diagnostic test accuracy in the emergency department and found it no better than simple performance based assessments (Carpenter et al., 2011a, Carpenter et al., 2011b). The AD8 has been reported to predict in-hospital delirium (Zeng et al., 2014) but has not previously been validated to recognise dementia in a hospital population.

The AD8 takes up to 5 minutes for the informant to complete.



## AD8 Dementia Screening Interview

Patient ID#: \_\_\_\_\_

CS ID#: \_\_\_\_\_

Date: \_\_\_\_\_

Remember, "Yes, a change" indicates that there has been a change in the last several years caused by cognitive (thinking and memory) problems.	<b>YES, A change</b>	<b>NO, No change</b>	<b>N/A, Don't know</b>
1. Problems with judgment (e.g., problems making decisions, bad financial decisions, problems with thinking)			
2. Less interest in hobbies/activities			
3. Repeats the same things over and over (questions, stories, or statements)			
4. Trouble learning how to use a tool, appliance, or gadget (e.g., VCR, computer, microwave, remote control)			
5. Forgets correct month or year			
6. Trouble handling complicated financial affairs (e.g., balancing checkbook, income taxes, paying bills)			
7. Trouble remembering appointments			
8. Daily problems with thinking and/or memory			
<b>TOTAL AD8 SCORE</b>			

**Figure 2-3: The AD8 as presented to participants**

## 2.1.5.3 Strengths and limitations of informant tools

The advantage of both informant tools, as opposed to traditional performance based tools is that they negate some of the bias associated with pre-existing educational background, cultural or language difficulties. They can also be used in situations where it is not possible to directly test the subject, such as in delirium, but also in severe illness, stroke, or in those with severe sensory impairment. Both tools have been validated for use over the telephone as well

as in person. However, they rely on the recall from the informant, and characteristics of the informant may influence the result such as depression or cognitive impairment. They also rely on the availability of an informant. A decline in the subject's physical function can also influence the informant's responses as reduced physical function can lead to a reduced ability to perform the tasks in the tools.

### 2.1.6 Participant data collection

Once recruited the following data was collected: disease severity was assessed using the Acute Physiology and Chronic Health Evaluation II (APACHEII)(Knaus et al., 1985) score; the Charlson Co-morbidity Index (Charlson et al., 1987) was used to assess for the burden of co-morbidity and the Rockwood Frailty Index (Rockwood et al., 2005) used to assess frailty. Urea/creatinine ratio, serum sodium, albumin and C-reactive protein (CRP) was collected from admission data.

### 2.1.7 Delirium phenomenology

Delirium severity and motor subtype were recorded at the time of recruitment

#### 2.1.7.1 Delirium Severity

Delirium severity was measured using the Delirium Rating Scale Revised version (DRSR-98) (Trzepacz et al., 2001). The DRSR-98 is a revision of the Delirium Rating Scale, a ten-item scale of symptoms of delirium to detect delirious subjects (Trzepacz et al., 1988). The DRSR-98 is made up of 16 domains of delirium symptomatology, of which three items are diagnostic items. Each item is rated 0 to 3 depending on the severity of the individual symptom. The scores are summed at the end. As this was used as a measure of delirium severity, the diagnostic domains were excluded. Therefore, 13 items were scored with total

scores ranging from 0 to 39. The symptom domains are: sleep–wake cycle disturbance, perceptual disturbances, delusions, lability of affect, language and thought process abnormalities, motor agitation or retardation, orientation, attention, short and long-term memory, and visuospatial ability. Higher values represent more severe delirium.

#### 2.1.7.2 Motor Subtype

The motor subtype of delirium was classified using the clinical assessment during screening and elements of the DRSR-98. These elements were used to classify subtype against the well-understood description by Meagher and colleagues (Meagher and Trzepacz, 2000). The motor actions of subjects with regard to frequency of action and speed of action were both observed, and information gathered from history gained from the informant and nursing staff. Participants were classified as hyperactive, hypoactive or mixed.

#### 2.1.8 Inpatient follow-up

Participants were followed up during their inpatient stay with review every 48 hours (Monday, Wednesday and Friday). On review, the presence of delirium was again assessed using the previous screening methods and a diagnosis of delirium made using DSM-IV-TR criteria. This allowed for the duration of delirium to be recorded. If participants were recorded as no delirium, but subsequently developed delirium again, the number of days with delirium was recorded as delirium duration. On discharge from hospital, the length of inpatient stay, discharge destination and any mortality was recorded.

#### 2.1.9 3 month follow-up interview

At three months after admission, a follow-up visit was arranged. Before contact was made, the electronic record was reviewed to note any mortality since discharge. If the participant

was still alive the participant and informant were contacted to arrange the follow-up visit. This was usually done through telephone contact. If the participant was in a new care home this was recorded. The number of days of any re-admission to hospital was recorded.

The follow-up visit comprised a structured interview and an examination to determine a diagnosis of dementia as well as outcome status. Interviews were offered at the participant's place of residence and lasted one hour. The informant was usually present, as was a care home staff member if the visit was in a care home. Initially a screen for delirium was carried out to detect persistent delirium using DSM-IV-TR criteria, as described in section 2.1.2. If no delirium was present then a thorough clinical history was taken from the participant and informant and a focussed examination carried out. Detailed cognitive assessment was carried out using the Addenbrooke's Cognitive Examination III (ACEIII).

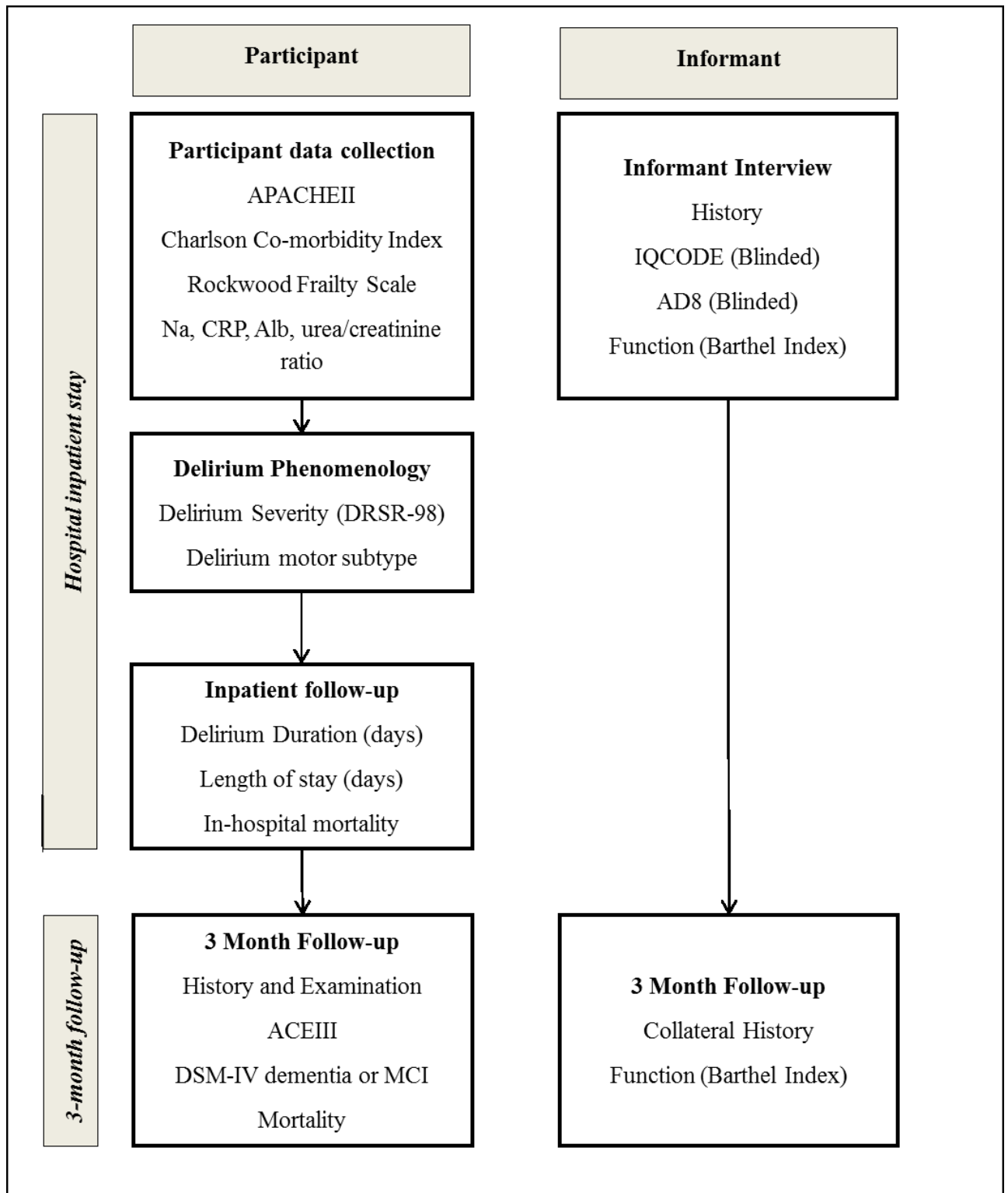
The ACEIII is the third version of the Addenbrooke's Cognitive Examination (Mathuranath et al., 2000) that was originally designed to detect mild dementia as well as to discriminate between Alzheimer's type dementia and fronto-temporal type dementia. It is a detailed cognitive test that examines five core cognitive domains: attention, memory, verbal fluency, language and visuospatial function. The ACE also incorporated the Mini-mental State Examination (MMSE). It requires a pen and paper and takes about 20 minutes to complete. Scores are given with a highest possible score of 100, with lower scores indicating worse cognitive function. The ACE was revised in 2006 (ACE-R), and a further revision took place in 2012 to remove the elements of the MMSE. Both the ACE and the ACE-R have been validated to distinguish between those with and without cognitive impairment, at a cut-off of 88. However, the cut-off for distinguishing between cognitive impairment and dementia is not clear, with cut-offs ranging between 75 and 88 reported in nine studies identified in a

systematic review (Crawford et al., 2012). The third version (ACEIII) was used and this has been validated against reference standards and its predecessor to detect dementia (Hsieh et al., 2013).

#### 2.1.10 Cognitive diagnosis at 3 months

Using information from the interview, examination and cognitive assessment diagnosis of either (1) probable dementia with subtype, (2) mild cognitive impairment or (3) no dementia was made. Dementia and subtype were diagnosed using the DSM-IV criteria (American Psychiatric Association, 1994) as discussed in detail in 1.1.3.1: (1) the development of multiple cognitive deficits, including memory impairment, and (2) the impairment is sufficiently severe to cause impairment in occupational or social function. MCI was diagnosed using the current consensus definition (Winblad et al., 2004): (1) the person is neither normal nor demented, (2) there is evidence of cognitive decline, and (3) that activities of daily living are preserved and complex instrumental functions are either intact or minimally impaired. To make the diagnosis of either dementia or MCI at the index admission the symptoms of cognitive decline had to have been present for at least 6 months prior to the admission with delirium. It is not possible to diagnose DSM-IV dementia in the presence of delirium so follow-up at three months was chosen as the best balance to allow recovery from delirium and ensuring an accurate diagnosis of dementia at the index admission.

These measures are summarised in Figure 2-4



**Figure 2-4: Flow chart of measure undertaken throughout course of the study**

## 2.2 Laboratory analysis

### 2.2.1 Blood sample collection and preparation

Serum samples were collected by venepuncture from participants the day after recruitment between 8am and 10am. Two 6ml plain tubes with clot activator were taken. Immediately after collection, the plain tubes were spun for 10 minutes at 3000rpm at room temperature to prepare serum (Eppendorf 5804R centrifuge). 200µl of serum was aliquoted into three 96-well plates for future batch analysis and the remainder as aliquots into cryovials. All samples were then stored at -80°C.

### 2.2.2 Analysis of cortisol and dehydroepiandrosterone sulphate (DHEAS)

To determine cortisol and DHEAS concentrations in serum an enzyme linked immunosorbent assay (ELISA) was performed using commercial kits (IBL International GMBH).

#### 2.2.2.1 Cortisol ELISA

Serum samples, as prepared in 2.2.1 were defrosted overnight in a cold room at 4°C, and then centrifuged at 1200 rpm (Eppendorf 5804R centrifuge). Wash buffer was prepared by diluting 100ml of wash buffer with 900ml of distilled water. 20µl of sample or standard was added to the ELISA plate and 200µl of enzyme conjugate was then added into each well. The plate was covered and mixed using a slow vortex. The plate was then incubated at room temperature for 60 minutes. After incubation the plate was washed three times using wash buffer and excess solution removed. 100µl of 3,3',5,5'-Tetramethylbenzidine (TMB) substrate was then added to each well, and incubated in the dark at room temperature for 15 minutes. After this 100µl of TMB stop solution was added to each well.

The optical density (OD) was then measured on a photometer (BioTek EL808) at 450nm. Using a standard curve of known cortisol concentrations, cortisol concentrations within the test samples were extrapolated using GraphPad Prism® software (GraphPad Software Limited, California, USA).

#### 2.2.2.2 DHEAS ELISA

To determine the concentration of DHEAS in the serum of participants with delirium, the same procedure in 2.2.2.1 was used except 25µl of serum was used instead of 20µl.

### 2.2.3 Analysis of cytokine concentration

To determine serum concentrations of pro-inflammatory and anti-inflammatory cytokines a multiplex immunoassay was used. Multiplex technology allows the analysis of multiple analytes from a single sample. The principle of the Bio-Rad magnetic bead array is that capture antibodies are coupled to a group of fluorescently-tagged magnetic beads. These capture antibodies bind with the antigen in the test sample. A detector antibody is then added to bind with the capture antibody-antigen complex coupled to a fluorescent reporter, streptavidin, to quantify the amount of captured antigen. A flow cytometer is then used to distinguish between the different beads based on their fluorescence intensity.

Serum samples, as prepared in 2.2.1, were defrosted overnight at 4°C. Samples were then centrifuged at 1200 rpm (Eppendorf 5804R centrifuge) for 2 minutes to remove sediment. Multiplex assay was performed according to manufacturer's instructions (Life Technologies) to determine the concentrations of the following cytokines: IL-1, IL-1RA, IL-6, IL-8, IL-10 and TNFα.



To prepare the assay, standards were reconstituted to 500µl and incubated on ice for 30 minutes. Then a standard 1 in 4 dilution was completed. Test samples were then also diluted 1 in 4 with sample diluent. Finally, 288µl 10x coupled beads were diluted with 5463µl assay buffer to a total volume of 5750µl to make the bead stock. To run the assay a 96 well plate was used. 50µl of bead stock was added to each well and then washed twice with 100µl of wash buffer. 50µl of sample, standards and blanks were then added to each well. The plate was covered to protect from light and incubated for 30 minutes on an orbital shaker (speed 850 rpm; Grant Instruments Limited, Cambridge, UK).

Detection antibodies were prepared using 150µl of 10x biotinylated detection antibody with 2850µl of detection antibody diluent. After incubation the plate was washed three times using 100µl of wash buffer. 25µl of biotinylated detection antibody was then added to each well and the plate covered to protect from light and incubated for 30 minutes on the orbital shaker. During the second incubation, 60µl of 100x streptavidin- R-Phycoerythrin (SA-PE) was diluted with 5940µl of assay buffer. After incubation, the plate was washed three times using 100µl of wash buffer. 50µl of SA-PE solution was added to each well and the plate incubated for a further 10 minutes (orbital shaker, speed 850 rpm). After the final incubation, the plate was washed three times in 100µl of wash buffer and the beads re-suspended in 125µl of assay buffer.

Cytokine concentrations were then analysed using a Bioplex 200 instrument (Luminex® Corporation, Austin, Texas, USA) running Bioplex Manager software version 6.1.

## 2.3 Power calculation and sample size

The primary aim of the study was to evaluate the diagnostic accuracy of the IQCODE against the gold standard of DSM-IV dementia diagnosis, and the sample size calculation was based on this. The power calculation was based on the method recommended by Guyatt et al. (Guyatt, 2005) using a sensitivity of the IQCODE of 80%, with 95% confidence intervals no wider than 10%. Using the formula  $0.1 = 1.96 \times \sqrt{pq} \div n$  where  $p$ =the proportion of target-positive patients with a positive test result, and  $q=1-p$ , figures were generated for  $n$ , which is the number of patients with the target disorder according to the gold standard which needed to be recruited. If the IQCODE performed with 80% sensitivity, 62 patients with a diagnosis of dementia were needed. If the test performed at 90% sensitivity, 35 would need to be recruited.

From previous estimations, it was assumed half of those with delirium would have dementia, so therefore 124 patients was the recruitment target.

## 2.4 Permissions

The protocol was assessed and approved by the Bradford Ethics Committee, part of the Yorkshire and Humber National research and Ethics Service (Ref: 12/YH/0534) on 9/1/13. National Health Service Research and Development permissions were granted on 11/1/13 (ref: RRK4658) by the [REDACTED] Research Governance Office.

A substantive amendment to the protocol was granted on 6/3/13 (Ref: 12/YH/0534 amendment 1). This amendment involved the changing of the originally planned screening tests.

## 3 Undiagnosed prior cognitive impairment in older people with delirium

### 3.1 Introduction

Delirium is an acute neuropsychiatric syndrome characterised by an acute change in cognition, attentional deficits and altered arousal (Inouye et al., 2014). It accounts for 20% of unplanned hospital admissions in older people (Siddiqi et al., 2006) and is associated with increased mortality and new institutionalisation (Witlox et al., 2010).

In contrast dementia is a chronic neurodegenerative disease characterised by progressive cognitive change, amnesic deficits and functional decline (Bayer, 2010). It is common in the general hospital setting, affecting up to 40% of unplanned hospital admissions (Sampson et al., 2009). According to research up to half of all patients with dementia admitted to hospital have no previous diagnosis. This masks considerably the true demand of dementia on unplanned hospital care (Sampson et al., 2009). Older people with dementia admitted to general hospitals also have increased adverse events (Mecocci et al., 2005) and higher mortality (Sampson et al., 2013).

Mild cognitive impairment (MCI) is the syndrome of reported memory loss and measurable cognitive deficit, which is not severe enough to affect activities of daily living. It is common, and is associated with a 5-10% yearly risk of development into dementia. (Mitchell and Shiri-Feshki, 2009). MCI has been identified as a risk factor for delirium (Kazmierski et al., 2014) however little is known about the prevalence of MCI in general hospital or in people with delirium.

People with dementia, compared to similar people without dementia, are six times more likely to be admitted to hospital with delirium (Ahmed et al., 2014). Given the high proportion of undiagnosed dementia generally in acutely hospitalised patients, it was hypothesised that patients with delirium are likely to have an especially high prevalence of undiagnosed dementia.

A systematic review of the reported prevalence of delirium superimposed on dementia was published in 2002 (Fick et al., 2002). Using the search terms in the review the search was re-run in Medline from 2002 to present. From these two sources eight individual cohort studies of medical inpatients (reported in 10 papers) where the prevalence of dementia in older people with delirium was reported, were identified. The prevalence of dementia in older hospital patients with delirium ranged from 51% to 68%. The pooled prevalence was 65.8% (95% CI 62.9-68.7), where 649 participants had delirium from 985 participants with dementia. These studies are summarised in Table 3-1.

**Table 3-1: Identified cohorts describing the prevalence of dementia in older medical patients with delirium.**

Study	Cohort	Delirium	Dementia in cohort of delirium	Proportion
Rockwood 1999	Acute admissions >65 Canada	38/202 with delirium DSM-IV	22/38 with dementia Recorded Diagnosis	58%
McCusker 2001, 2002	Acute admissions >65 Canada	243/361 with delirium CAM	166/243 with dementia IQCODE >3.5	68%
White 2005	Acute general hospital >75 UK	105/283 delirium DSM-IV	63/105 probable dementia using IQCODE and collateral history	60%
Laurilla 2008	Acute geriatric ward and nursing home >70 Finland	106/425 with delirium DSM-IV	66/106 with dementia Consensus diagnosis	62%
Ryan, Maegher 2013	Acute general hospital, >18 Ireland	55/331 with delirium DSM-IV	28/55 with cognitive impairment IQCODE telephone	51%
Morandi 2014	Rehabilitation patients >65 Italy	323/2642 with delirium DSM-IV	213/323 with dementia DSM-III	66%
Tay 2014	Delirium specialist ward >65 Singapore	All with delirium – 122 CAM	82/122 with dementia Carer interview and DSMIV	67%
Whitamore 2014	Acute general hospital >70 UK	27% delirium DRDR-98	72/107 with dementia Previous history	68%
POOLED			649/985	65.8% (95% CI 62.9-68.7)

The following chapter aims to answer the first key question of this thesis; what is the prevalence of cognitive impairment (dementia and mild cognitive impairment) in older people with delirium? It will address this question by attempting to identify accurately the proportion of people with delirium admitted unplanned into hospital with delirium, with both previously diagnosed and undiagnosed dementia and mild cognitive impairment.

## 3.2 Methods

### 3.2.1 Participant recruitment

Unselected patients aged 70 years and over with an unplanned medical admission and delirium were recruited. The recruitment process was described in detail in section 2.1.

In brief, between March 2013 and November 2014 admissions were screened by the author for delirium. Participants were eligible for the study if they met the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV-TR) criteria for delirium.(American Psychiatric Association, 2000). The screening took place on 143 days evenly spread over the period. Patients with delirium were then invited to participate. Informed consent was sought from the potential participant if they had the mental capacity to give it and for those who lacked the mental capacity to give informed consent, the next of kin (NOK) was consulted. The NOK were also asked to agree to act as informants.

Potential participants who were unable to communicate because of severe sensory impairment or non-competence in English were excluded, as were those deemed to be at risk of imminent death.

An informant interview elicited a previous diagnosis of dementia or cognitive impairment, as well as a history of prior cognitive function. No new diagnoses of dementia were made at baseline due to the difficulties of distinguishing dementia from delirium in the presence of the latter.

### 3.2.2 3-month cognitive assessment

At 3 months, a follow-up assessment was undertaken in survivors, at the patient's own home or hospital if they were still an in-patient, by the same assessor who had seen them at baseline. The follow-up assessment is described in more detail in section 2.1.9. The presence of persistent delirium was first established using DSM-IV-TR criteria. If no delirium was present, the presence or absence of dementia or MCI was diagnosed. To make the diagnosis of either dementia or MCI at the index admission the symptoms of cognitive decline had to have been present for at least 6 months prior to the admission with delirium. It is not possible to diagnose DSM-IV dementia in the presence of delirium so follow-up at three months was chosen as the best balance to allow recovery from delirium to ensure an accurate diagnosis of dementia at the index admission.

The chapter results are reported using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guidelines. (von Elm et al., 2008).

### 3.2.3 Statistics

Descriptive statistics were used to describe the proportions of cognitive diagnoses given to the cohort with 95% confidence interval calculated. Differences between common clinical variables were analysed, using the independent t-test, Kruskal-Wallis test or chi-squared test depending on the normality of the variables and whether the variables were continuous or

categorical. Odds ratios to predict the risk of having previously undiagnosed dementia were calculated using univariate binary logistic regression.

### 3.3 Results

1327 older people admitted to hospital were screened for delirium between March 2013 and November 2014. Of these, 228/1327 (17.2%) were diagnosed with DSM-IV-TR delirium. 125 of 228 (54.8%) were recruited. The main reason for non-recruitment was lack of an available next of kin to act as consultee and informant (57/103).

Of the 125 recruited, 45 (36%) had a previously recognised diagnosis of dementia. The diagnosis was made by a GP in 4/45 (8.9%) cases, a geriatrician in 7/45 (15.5%) cases and an old age psychiatrist in 34/45 (75.6%) cases. 32/45 (71.1%) had been assessed in a memory clinic and 17/45 (37.8%) were on cognitive enhancing drugs.

Of the 125 recruited, 82 (66%) were followed up at 3 months: 25 (20%) had died, 10 (8%) declined the follow-up visit and eight (6%) were not contactable. There was no difference in age, gender or admission dementia status between those followed up and those not.

The mean age of the followed up sample was 84.4 years and 65.9% were female. 21/82 (24.4%) were from a care home. Figure 3-1 shows participant flow.



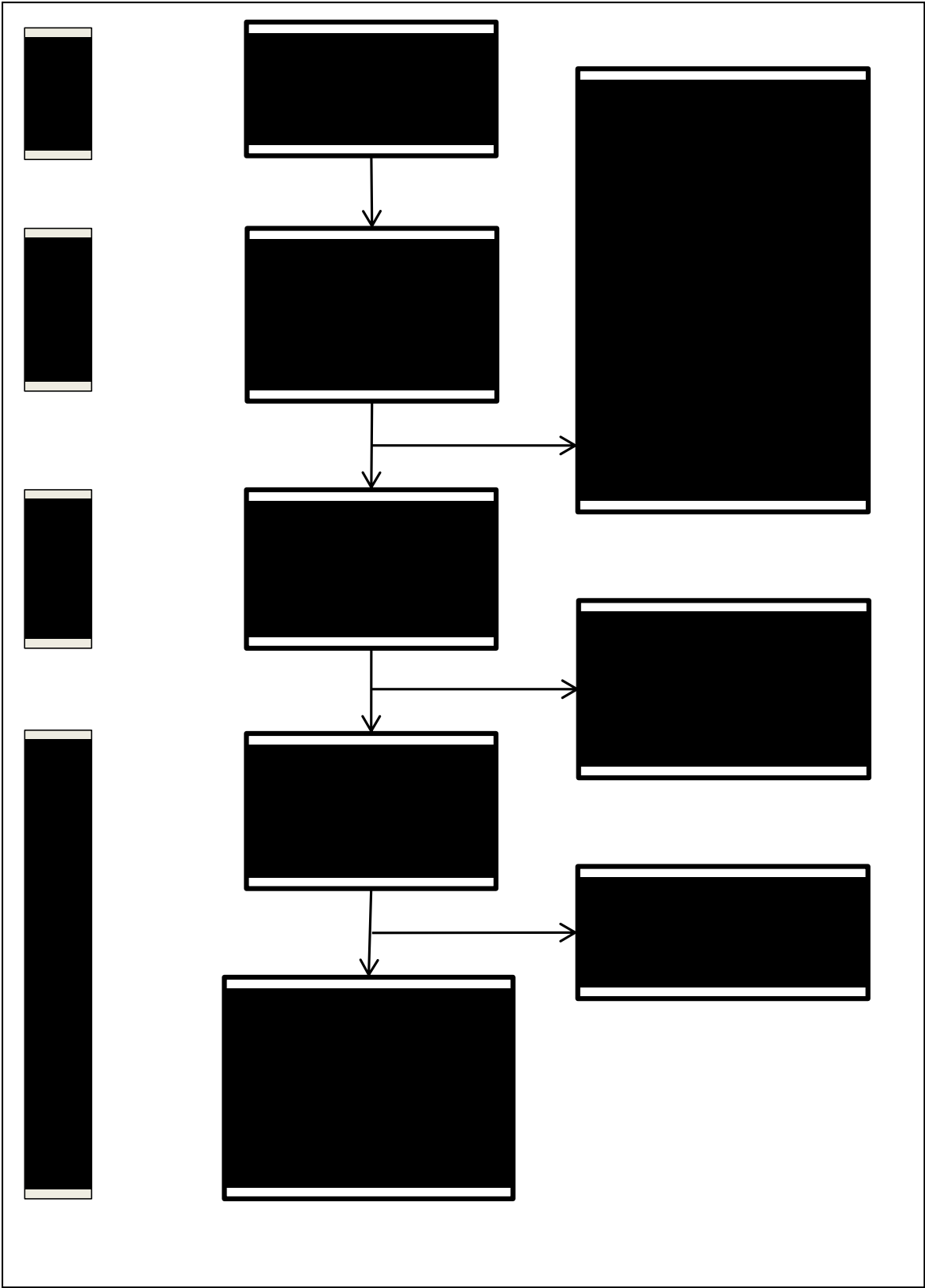
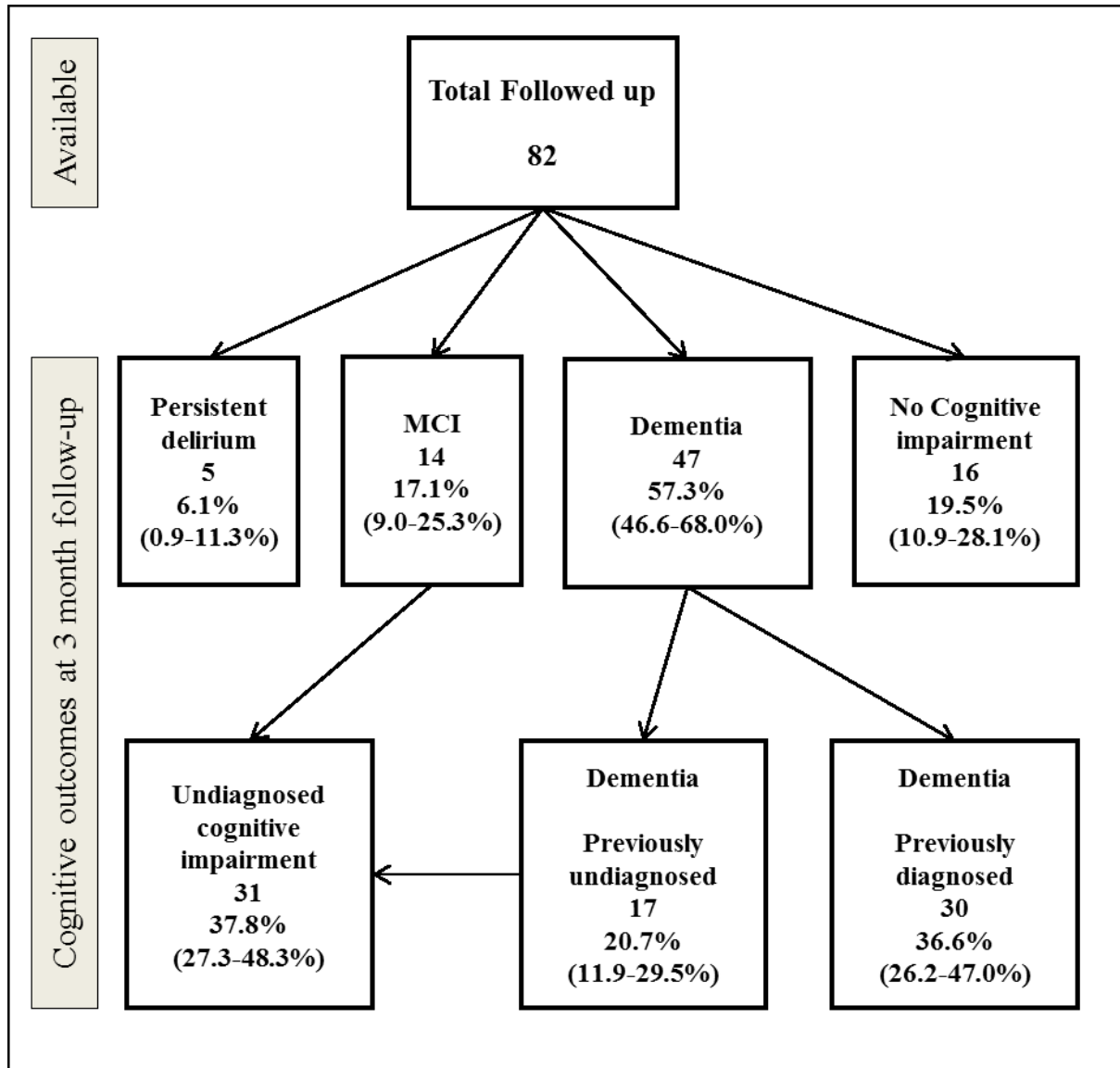


Figure 3-1: Flow chart showing participant flow through the study

At 3 months 5/82 (6.1%) had persistent delirium, 14/82 (17.1%) were diagnosed with MCI, 47/82 (57.3%) were diagnosed with dementia and 16/82 (19.5%) had no evidence of prior cognitive impairment. Of the 47 with dementia, 31/47 (66%) had Alzheimer's disease, 12/47 (25.5%) had vascular dementia, 3/47 (6.4%) had mixed dementia and 1/47 (2.1%) had dementia with Lewy bodies. 17 (20.7%) had probable dementia that was present at index admission but not diagnosed. MCI had not been previously diagnosed in any of those in whom it was diagnosed at the 3-month follow up. Of these newly diagnosed cases, 12 were diagnosed with Alzheimer's disease and five with vascular dementia. In total, 31/82 (37.8%) patients who had been admitted to hospital with delirium had a previously undiagnosed diagnosable cognitive impairment. Figure 3-2 illustrates these proportions with 95% confidence intervals.



**Figure 3-2: Diagnosis of cognitive disorders at 3 months in participants with delirium**

The group with cognitive impairment had a higher burden of co-morbidity (median co-morbidity index 2.0 vs 0.0,  $p=0.002$ ) and frailty (median clinical frailty scale 5.5 vs 4.0,  $p<0.0005$ ) than the group with no prior cognitive impairment. The demographic data in presented in Table 3-2.

**Table 3-2 Table reporting demographic and illness data of patients organised by cognitive outcome.**

	Cognitive impairment at 3 months						Difference
	Persistent delirium N=5	MCI N=14	Dementia – previously diagnosed N=30	Dementia – not previously diagnosed N=17	Combined cognitive impairment N=66	No cognitive impairment N=16	
Age Years, mean, SD	84.4±3.7	82.7±5.0	84.6±6.5	87.2±7.0	84.4±6.5	82.3±7.6	NS
Gender % female	20.0	64.3	76.0	64.7	66.7%	62.5	NS
Disease severity (APACHEII) Median, IQR	9 (5)	9.5 (8)	9 (5)	8 (4)	9 (5)	10.5 (7)	NS
Charlson co-morbidity index Median, IQR	3 (3)	1.5 (3)	2 (2)	2 (2)	2 (2)	0.0 (2)	.002 *
Rockwood clinical frailty Median (IQR)	6 (4)	5 (1)	6 (1)	6 (2)	5.5 (1)	4(2)	<0.0005*
Cognitive assessment (ACEIII) Mean, SD	NA	66.4 (8.7)	20.1 (23.7)	29.4 (26.5)	33.2 (28.7)	86.8 (7.2)	<0.0005*

MCI=mild cognitive impairment, ACEIII = Addenbrooke's Cognitive Assessment III, carried out at 3 month follow-up, Difference = Difference between cognitive impairment and no cognitive impairment, using independent samples Kruskal-Wallis test as data not normally distributed, NS=not significant, \*=statistically significant.

When comparing those with diagnosed dementia to those with previously undiagnosed dementia there was no significant difference between age, gender, co-morbidity, frailty or cognitive assessment. None of these variables was able to predict who had unrecognised dementia using univariate logistic regression. This is illustrated in Table 3-3.

When trying to predict unrecognised dementia at admission from the group admitted with no recognised diagnosis of dementia, age and frailty were significantly associated with having unrecognised dementia. Every increased year of age was associated with a 12% increased risk of having unrecognised dementia (OR 1.12, 95% CI 1.01-1.25) and every increased point in the Rockwood clinical frailty scale was associated with a two and a half fold increased risk of having unrecognised dementia (OR 2.58, 95% CI 1.34-4.97). This is illustrated in Table 3-4.

**Table 3-3: Comparison between those with previously diagnosed dementia and those with previously undiagnosed dementia**

	Dementia – previously diagnosed N=30	Dementia – not previously diagnosed N=17	p	OR (95% CI)
Age Years, mean, SD	84.6±6.5	87.2±7.0	0.143	1.06 (0.97-1.17)
Gender % female	76.0	64.7	0.378	0.56 (0.15-2.06)
Disease severity (APACHEII) Median, IQR	9 (5)	8 (4)	0.176	0.94 (0.76-1.15)
Co-morbidity (Charlson co- morbidity index) Median, IQR	2 (2)	2 (2)	0.784	0.85 (0.53-1.36)
Frailty (Rockwood clinical frailty scale) Median (IQR)	6 (1)	6 (2)	0.398	0.86 (0.51-1.46)
Cognitive assessment (ACEIII) Mean, SD	20.1 (23.7)	29.4 (26.5)	0.297	1.02 (0.99-1.04)

**Table 3-4: Comparison of those with previously undiagnosed dementia, with those on admission with no previous dementia diagnosis on admission to hospital.**

	Dementia – not previously recognised N=17	No previous dementia diagnosis N=33	p	OR (95% CI)
Age Years, mean, SD	87.2±7.0	82.6±6.2	0.02 *	1.12 (1.01-1.25) *
Gender % female	64.7	57.6	0.63	1.35 (0.40-4.50)
Disease severity (APACHEII) Median, IQR	8 (4)	10 (6)	0.16	0.90 (0.76-1.07)
Co-morbidity (Charlson co- morbidity index) Median, IQR	2 (2)	1 (3)	0.10	1.18 (0.84-1.67)
Frailty (Rockwood clinical frailty scale) Median (IQR)	6 (2)	4 (2)	0.002*	2.58 (1.34-4.97)*

### 3.4 Discussion

Three quarters (61/82, 74.4%) of patients admitted to hospital with delirium had evidence of prior cognitive impairment. In 31 (51% of those with prior cognitive impairment and 37% of all patients admitted to hospital with delirium) this cognitive impairment had been previously

undiagnosed – in 14 cases dementia had been undiagnosed and in 17 cases mild cognitive impairment had been undiagnosed. Age and frailty predicted previously undiagnosed in admissions to hospital with no previously recognised diagnosis.

The study did not recruit all patients admitted to hospital with delirium. There was no difference between the age or sex of those who were and were not recruited, so this is unlikely to have caused a significant bias in the results. The main reason for non-recruitment was a lack of a consultee / informant. Recognising the difficulty of separating delirium from dementia, strict reference criteria were applied for the diagnosis of delirium and dementia.

The findings are in line with previous studies of delirium. The prevalence of dementia was 57% of patients with delirium, in keeping with previous reports (51-68%) (Ryan et al., 2013, Whittamore et al., 2014). Delirium was diagnosed on admission in 17.1% of older people in the cohort, which also is in keeping with previously reported delirium prevalence rates (15-25%) (Siddiqi et al., 2006, Collins et al., 2010).

As part of a study measuring drug metabolism in older patients with delirium, 'probable dementia' was recorded using an informant questionnaire (Informant questionnaire of cognitive decline in the elderly, IQCODE) and informant interview (White et al., 2005). This assessment was carried out at the time of admission. They report that 63/105 patients with delirium had probable dementia, and only 26/63 had a previous diagnosis of dementia made by a geriatrician or psychogeriatrician. Therefore 37/105 (35%) of this cohort had unrecognised probable dementia. A further study has reported the proportion of undiagnosed cognitive impairment in delirium, reporting that in only five of 28 participants with delirium and cognitive impairment was a diagnosis of dementia recorded in the medical notes (Meagher et al., 2014b). Here the IQCODE was used to classify previous cognitive



impairment and was administered over the telephone. However, no previous studies have reported the proportion of cases of delirium who have undiagnosed dementia at presentation diagnosed by a reference standard, and none have previously reported the prevalence of prior mild cognitive impairment patients presenting with delirium.

The significance of the novel finding of a high proportion of people with delirium having prior undiagnosed cognitive impairment is that, not only is delirium an important diagnosis to make in older patients admitted to hospital (MacLulich et al., 2013), but it is also an opportunity to identify serious and previously unrecognised mental health conditions (Russ et al., 2012). Routine follow up of patients who have presented with delirium could be of value - to identify those with persisting delirium as well as to identify previously unrecognised dementia and mild cognitive impairment. Such patients could then be counselled, advised and supported or offered the opportunity to participate in research – which would not be possible without these diagnoses being recognised. Diagnosing patients with dementia also allows identification of those who would benefit from pharmacological therapy (van de Glind et al., 2013). There is a government drive to improve dementia diagnosis rates through the National Dementia Strategy (Burns and Robert, 2009) and the Prime Minister’s dementia challenge (Kmietowicz, 2012), but similar activities are worldwide. Further work is now required to develop follow-up procedures to do this, and to evaluate their cost effectiveness. However, it may be that frailty is a key condition to identify as this may help predict those at risk of having undiagnosed dementia.

### 3.5 Summary

This chapter has attempted to answer the principal question; what is the prevalence of cognitive impairment (dementia and mild cognitive impairment) in older people with

delirium? By the recruitment of a cohort of older patients with delirium and ascertaining robust cognitive diagnosis at 3-month follow-up the prevalence of cognitive impairment has been described. The prevalence of dementia in older patients with delirium is 57.3% and the prevalence of MCI is 17.1%. The key finding is that one in five older people with delirium had dementia not previously diagnosed. This suggests delirium is a high-risk population to identify those with undiagnosed cognitive impairment.

A strategy to identify dementia in older people with delirium will be evaluated in the next chapter.

## 4 Screening for dementia in general hospital inpatients: A systematic review and meta-analysis of available instruments

The previous chapter identifies a high proportion of undiagnosed dementia in patients with delirium. The following chapter will report a systematic review and meta-analysis of available screening instruments for detecting dementia in older general hospital patients. The second readers were Dr Huma Naqvi of University Hospital Birmingham and Dr Bart Sheehan of the University of Warwick. The author devised the protocol and planned the organisation of the review. All readers contributed to reviewing articles, data extraction and contributed to data analysis. The following is exactly as published in *Age and Ageing* (2013 Nov;42(6):689-95) but with some minor formatting changes.

### 4.1 Introduction

Dementia affects about 36 million people worldwide, with numbers expected to double every 20 years to 66 million by 2030 (Alzheimer's Disease International, 2009). In the United Kingdom 700,000 people are affected, but it is estimated that only a third of people with dementia currently have been diagnosed. Improving diagnosis rates is a key aspect of the World Alzheimer's Report of 2011 (Alzheimer Disease International, 2011). Despite a drive in the neurosciences for biomarkers to detect early dementia (Genius et al., 2012) the ethics of when, or indeed whether to diagnose what is a progressive neurological disease remain difficult (Mattsson et al., 2010) and some take the view that diagnosis is of little benefit (Sharvill, 2012). This may reflect a negative view among clinicians of what can be done

therapeutically (Martinez-Lage et al., 2010), and the case for general population screening for dementia remains controversial (Brayne et al., 2007, Brunet et al., 2012).

There is potential value in diagnosis of dementia throughout the disease course. Diagnosis allows access to the appropriate support services as well as drug treatment. There is clinical evidence demonstrating drug efficacy in early dementia (Molinuevo et al., 2011, Gauthier, 2005). Earlier diagnosis may allow patients to make advance care decisions whilst still competent to do so. Diagnosis may also improve quality of life for carers by allowing access to dementia specific resources as well as providing an explanation for a persons altered mental state (Mittelman et al., 2007). Economically, in the UK early diagnosis would mean increased costs up front, although savings made through reduced institutionalisation and better care might result in overall costs savings and health benefits (Banerjee and Wittenberg, 2009, Getsios et al., 2012). Diagnosis is well accepted by patients with a survey of patients in a memory clinic showing that even patients with severe dementia would prefer to be told their diagnosis (Jha et al., 2001). Although diagnosis has benefits it should also be appreciated that it can have major psychosocial effects, both positive and negative (Bunn et al., 2012).

Dementia and cognitive impairment are common amongst older hospital patients and remain under diagnosed (Sampson et al., 2009, Torisson et al., 2012), in common with other mental health problems in the same group (Goldberg et al., 2012). In 2009 Sampson and colleagues showed that 42% of unselected older medical inpatients had dementia: half of these had not previously been diagnosed with dementia while mortality was much higher among those with dementia (Sampson et al., 2009). The diagnosis of dementia in general hospitals is also complicated by the complex diagnostic challenge of concurrent delirium, with up to two-thirds of people with delirium having concurrent dementia, and dementia itself being a

significant risk factor for the development of delirium (Fong et al., 2009b). The need to improve diagnosis of dementia in hospitals is long established (Arie, 1973). Medical admission could therefore offer a timely opportunity to identify potential cases of dementia. Recognition of dementia also allows for improved care during the hospital admission. Improved care may include avoiding new medical events known to be more likely among inpatients with dementia (Mecocci et al., 2005) accessing dementia services, planning legal and capacity assessments and involving family in care decisions (Russ et al., 2012).

There are many screening instruments in current use and guidelines exist on which tests to use. These are often not restricted to hospital use and may not be validated for hospital use. Current guidelines include the National Institute for Health and Clinical Excellence (NICE), who in their UK guidance on recognition of dementia suggest using the Mini Mental State Examination (MMSE) (Folstein et al., 1975), the 6 item cognitive impairment test (6-CIT) (Brooke and Bullock, 1999), the general practitioner assessment of cognition (GPCOG) (Brodaty et al., 2002) and the 7-minute screen (Solomon and Pendlebury, 1998) (National Institute for Health and Clinical Excellence, 2006). Guidelines from the American Geriatrics Society recommend using the Mini-Cog assessment instrument for dementia (Mini-cog) (Borson et al., 2000) followed by the MMSE or Montreal Cognitive Assessment (MOCA) (Nasreddine et al., 2005) if positive. A Further tool in common use is the Addenbrooke's Cognitive Assessment (Mioshi et al., 2006). The British Geriatrics Society suggests using the MMSE, the CLOX1, an executive clock drawing test (CLOX1) (Royall et al., 1998) and the Informant Questionnaire of Cognitive Decline in the Elderly (IQCODE) (Jorm and Jacomb, 1989), in conjunction with a delirium screen, to identify dementia specifically in medical inpatients (British Geriatric Society, 2005). All these professional guidelines

emphasise a two-stage approach; that is, detailed assessment after initial screening or clinical suspicion.

The aim of this review is to determine which of the instruments advocated for screening for dementia have been validated in older hospital inpatients and therefore inform decision making for services.

## 4.2 Search Strategy and Selection Criteria

An electronic database search of Embase, PsycINFO and MEDLINE was made for articles in English using search terms in the following 3 domains: Dementia and cognitive impairment, diagnosis and screening tests, and thirdly general hospital inpatients. Appendix 2 contains the full search strategy. The databases were accessed on 20/11/12 and Embase was searched from 1947, PsycINFO from 1967 and MEDLINE from 1946. Only English language articles were accessed due to lack of resources to translate. The abstracts were then screened by two assessors (TJ, HN) independently based on the following criteria and the full texts then retrieved if they:

- 1 Included patients studied during a hospital inpatient stay using a screening test for cognitive impairment or dementia. Patients studied in psychiatric wards, memory clinics and the community were excluded
- 2 Included an age defined group of older people (60 years or older)

Published review articles on cognitive screening were also examined to identify any further studies (Sheehan, 2012, Harwood, 2012, Young et al., 2011, Mitchell and Malladi, 2010b, Mitchell and Malladi, 2010a, Woodford and George, 2007, Cullen et al., 2007, Tombaugh and

McIntyre, 1992). An additional electronic search was done with each identified instrument as a key search term with the search terms for general hospital inpatients to identify any further validation studies. The reference sections of the selected papers were also studied as were relevant clinical guidelines.

The full texts of the selected studies were reviewed independently by three reviewers (TJ, HN and BS) against the following final inclusion criteria:

- 1 The study group are in-patients in general hospitals, and not in a psychiatric hospital, care home or the community.
- 2 Studies include older people (60 years or older) as the main subject group or a clearly defined sub-group.
- 3 The study uses a recognised screening instrument for cognitive impairment or dementia and this is compared with a 'gold' or reference standard. The reference standard was defined as the Diagnostic and Statistical Manual of Mental Disorders (DSM) versions III to IV (Association, 2000), International Classification of Diseases – 10<sup>th</sup> edition (ICD-10) (World Health Organisation, 1992), the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association Alzheimer's criteria (NINCDS-ADRDA) (McKhann et al., 1984) or expert diagnosis following interview.
- 4 At least 10 cases of dementia according to gold standard

From the selected papers the following data was recorded: Patient group and sample size, mean age and proportion female, prevalence of dementia, test used and cut off, comparator (gold standard), sensitivity and specificity. Any disagreements were decided by consensus.

Following previous convention, statistical analysis was done to produce a meta-analysis if there were 3 studies assessing the same test (Irwig et al., 1994). We used Meta-Disc version 1.4, a meta-analytical software package (Zamora et al., 2006) to produce a pooled sensitivity, specificity, positive likelihood ratio (LR +), negative likelihood ratio (LR -), diagnostic odds ratio (DOR) and a summary receiver operating characteristics analysis (SROC). Likelihood ratios are a measurement of diagnostic accuracy and say how likely a person with a condition is to have a positive test (LR+) or a person without the condition is to have a positive test (LR-). The diagnostic odds ratio is also a measurement of diagnostic accuracy independent of prevalence and represents the probability of the test being positive if a person has the disease relative to the odds of the test being positive if the person does not have the disease. Heterogeneity was measured by calculating I-square. The  $I^2$  index describes the variation across the studies that due to significant heterogeneity rather than random chance.

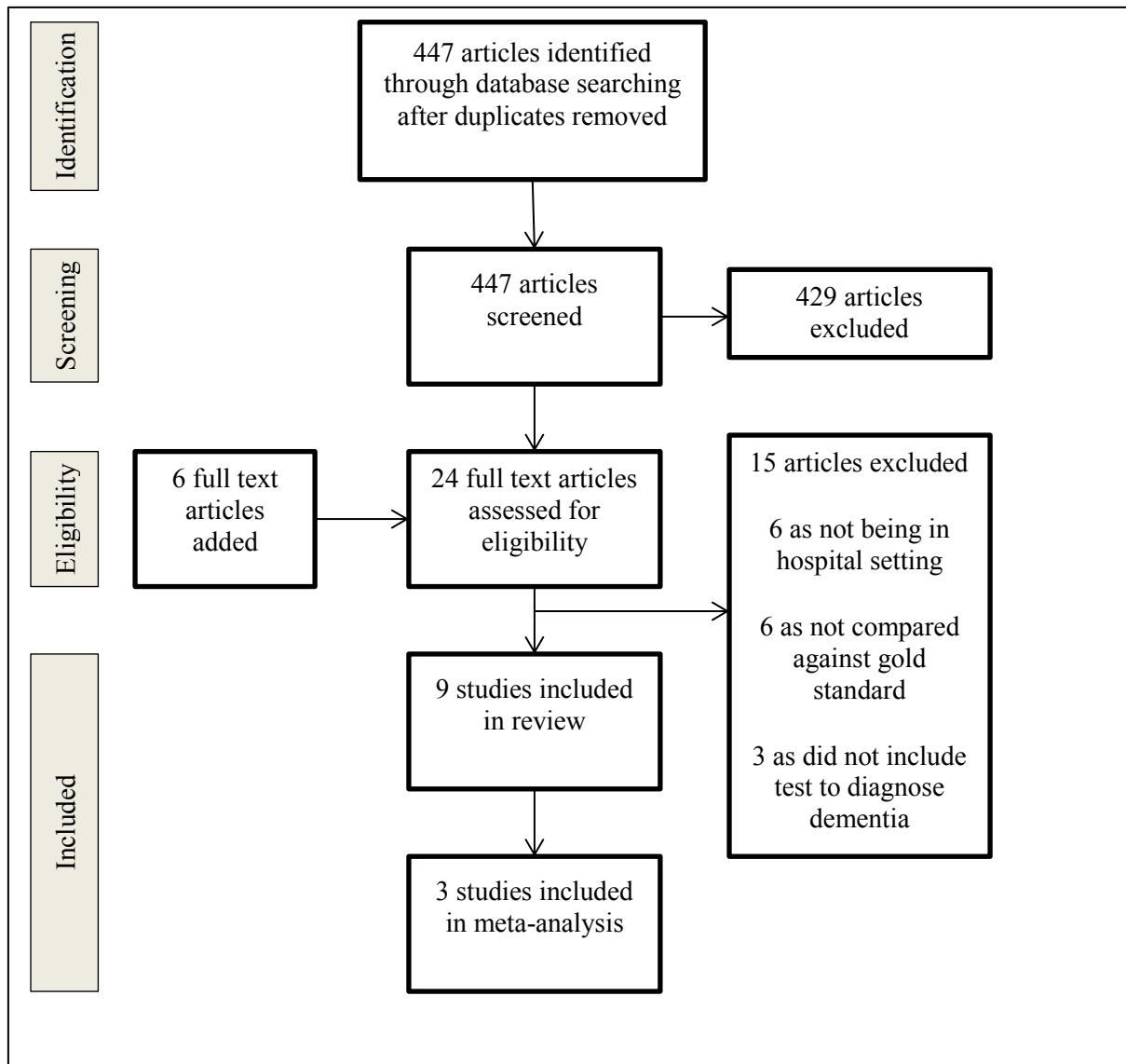
Selected studies were then reviewed against the QUADAS-2 criteria to assess the study quality and risk of bias (Whiting et al., 2011).

This work was supported jointly by the Research into Ageing Fund, a fund set up and managed by Age UK and the British Geriatric Society through a grant to TJ. They played no role in the design, execution, analysis and interpretation of data, or writing of the study.

## 4.3 Results

The initial search returned 447 articles of which 18 were selected. Three further articles were identified by the review articles selected and a further 3 identified by searching by specific tests. See Figure 4-1 for details.





**Figure 4-1: Flow diagram showing the selection of studies for the systematic review and meta-analysis**

Of those twenty four, nine studies met the inclusion criteria (O'Keeffe et al., 2011, Leung et al., 2011, Antonelli Incalzi et al., 2003, Inouye et al., 1998, Harwood et al., 1997, Jitapunkul et al., 1991, Erkinjuntti et al., 1987, Klein et al., 1985, Anthony et al., 1982). Six were excluded as the MMSE was used as the main comparator, Six were excluded as the setting was not exclusively the general hospital and three were excluded as they did not involve a test

to diagnose dementia. Six discrete instruments were investigated in the nine studies. The papers using a recognised gold standard diagnosis as comparator are shown in Table 4-1. The instruments studied were the Abbreviated Mental Test Score (AMTS), the Digit Span backwards test, the Time and Change Test, the Informant Questionnaire of Cognitive Decline in the Elderly short form (IQCODE), the Short Portable Mental Status Questionnaire (SPMSQ) and the Mini-Mental State examination (MMSE). Across the studies sensitivity ranges from 73% to 100% and specificity ranges from 65% to 99%. All the studies involved medical in-patients and dementia prevalence varies from 6% to 52.1%

**Table 4-1: Data from studies using the reference standard.**

Study and setting	Patient group, age and sample size	Mean age	% ♀	Comparator	Prev (%)	Test used and cut off	Sen %	Sp %
O'Keefe 2011 <sup>50</sup> Ireland	Medical inpatients Over 65 years, N=169	76, Range 65-101	58	Interview and expert opinion	37	Any error in year with orientation Any error in month with orientation	85 73	92 90
Leung 2011 <sup>51</sup> Hong Kong	Medical inpatients Over 75 years, N=144	80, no SD reported	46	DSM-IV	36	Digit span backwards Unable to complete 3 numbers	77	78
Antonelli Inclaz 2003 <sup>52</sup> Italy	Medical Inpatients N=2808	71, $\pm$ 0.27 SE	45	DSM-III-R	6.0	AMTS <7	81	84
Inouye 1998 <sup>53</sup> USA	Medical and surgical inpatients Over 70 years, N=776	78, $\pm$ 6.1 SD	55	Expert opinion using MMSE and BDRS	10	Time and change test Either component incorrect	86	71
Harwood 1997 <sup>54</sup> UK	Medical inpatients Over 65 years, N=201	76, range 65-97	51	DSM-III-R	10 dementia alone 13 dementia with delirium	AMTS <8 AMTS <7 IQCODE >3.44	96 83 100	73 83 86
Jitanpunkal 1991 <sup>55</sup> UK	Geriatric inpatients Over 60 years, N=168	82, $\pm$ 6.6 SD	59	DSM-III-R	35	AMTS <7 AMTS <8	81 91	85 75
Erkinjuntti 1987 <sup>56</sup> Finland	Medical inpatients Over 65 years, N=282	75, $\pm$ 7.2 SD	61	Interview and expert opinion	9.6	SPMSQ 3 errors	86	99
Klein 1985 <sup>57</sup> USA	Medical inpatients Over 40 years, but results quoted for >60 years	72 demented 66 non-demented	59	DSM-III	52	6 items from MMSE Error in one	91	85
Anthony 1982 <sup>58</sup> USA	Medical inpatients Over 20 years, but results quoted for >60 years N=97, N=41 for those >60	No mean age quoted	63	DSM-III	38 dementia and 'delirium with dementia' 14 dementia alone	MMSE <24 MMSE <23 MMSE <22	93 88 81	65 74 78

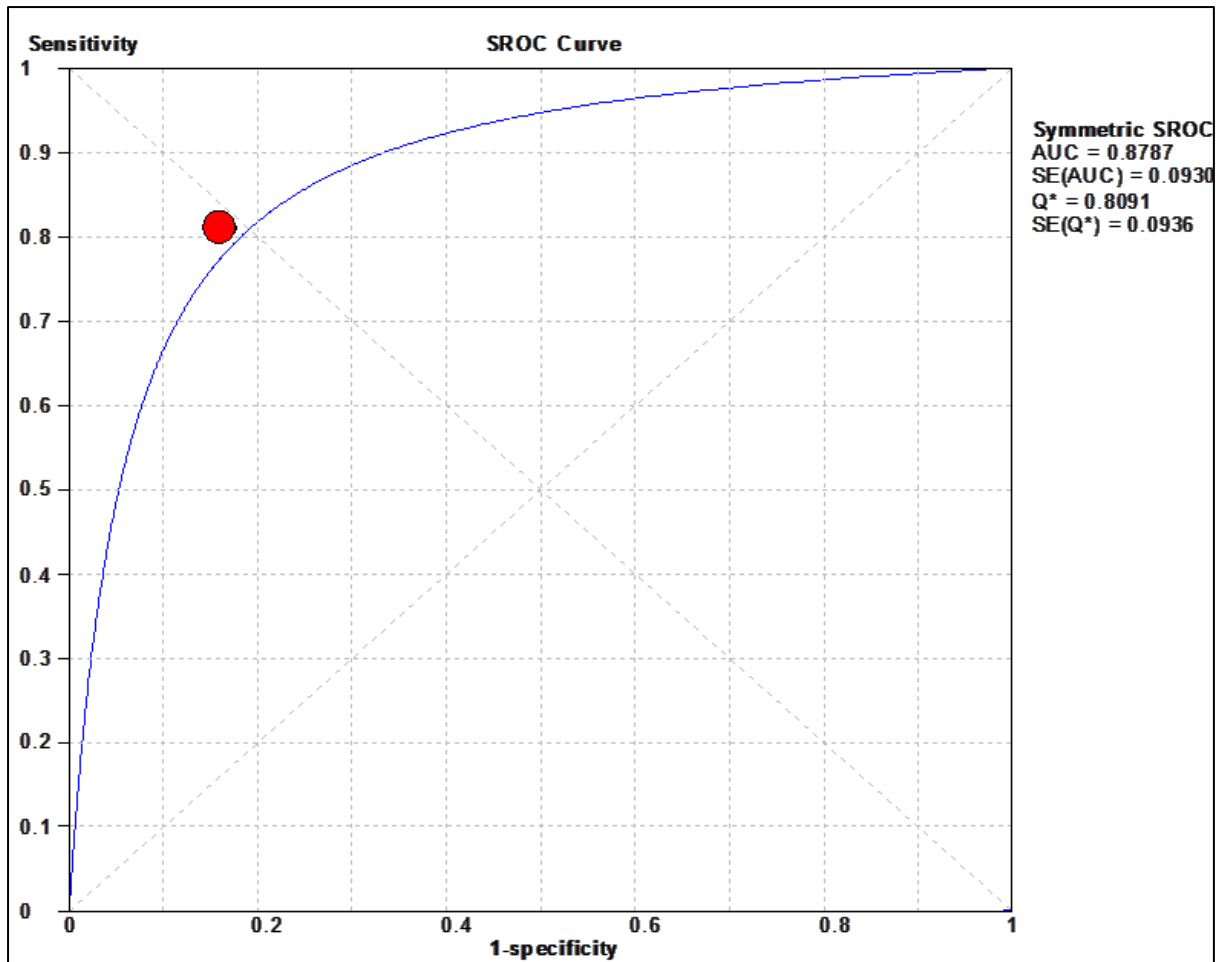
♀=female Prev=prevalence of dementia, Sen = sensitivity, Sp = specificity, SD = Standard deviation, SE = Standard error, DSM = Diagnostic and statistical manual of mental disorders, AMTS = Abreviated mental test score, IQCODE = Informant questionnaire of cognitive decline in the elderly, MMSE = Mini mental state examination, SPMSQ = Short portable mental status questionnaire

Meta-analysis of the 3 studies comparing the AMTS (cut-off value of  $<7$ ) with dementia as defined by DSM-III-R was performed (Table 2) (Antonelli Incalzi et al., 2003, Harwood et al., 1997, Jitapunkul et al., 1991). This showed an estimated prevalence of dementia of 7.8% with a sensitivity of 81%, Specificity of 84%, a positive likelihood ratio of 5.05, a negative likelihood ratio of 0.23 and a diagnostic odds ratio of 22.37. Figure 4-2 shows a summary receiver operating characteristic (SROC) for the three studies with an area under the curve of 0.88. SROC derivation and details of the  $Q^*$  are reported elsewhere (Rosman and Korsten, 2007).

**Table 4-2: Meta -analysis of data from Antonelli Inclaz 2003, Harwood 1997 and Jitanpunkul 1991, using the AMTS against Reference standard (DSM-III-R).**

Test and cut off	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)	DOR	I <sup>2</sup> (%) Across all	AUC
AMTS <7	0.81 (0.76-0.86)	0.84 (0.83-0.85)	5.04 (4.54-5.61)	0.23 (0.17-0.29)	22.45 (15.92-31.65)	0	0.88

LR+ = positive likelihood ration, LR- = negative likelihood ratio, DOR = Diagnostic odds ratio, I<sup>2</sup> = test of heterogeneity, AUC = area under the curve from a summary receiver operating characteristic curve



**Figure 4-2: Summary receiver operating characteristic for 3 studies using AMTS cut off of <7 against DSM-IIIIR dementia demonstrating an AUC of 0.87. The red circle represents the Q\*, where sensitivity equals specificity.**

Study quality and risk of bias assessed using QUADAS-2 is shown in appendix 2. There are two main concerns about potential risk of bias. Five studies did not blind the assessors' of the reference standard to the initial screening test result, and the index test threshold was not pre-specified in seven studies. All studies were otherwise well designed and there was no concern regarding the study applicability.

#### 4.4 Discussion

The number of studies we have reported is small, with only the AMTS (Hodkinson, 1972) having more than a single paper investigating its properties. We found only a single study

validating the full MMSE in hospital inpatients, despite this being a very common instrument and used as a 'reference' standard in six excluded studies. Predictably, as sensitivity increases, the specificity of MMSE reduces. With reference to the instruments recommended in the UK NICE guidelines the MMSE has been validated as described, and we could find no validation for the 6-CIT, GP-COG or 7-minute screen. From the American Geriatrics Society guidance, again only the MMSE has been validated in the hospital population. The British Geriatrics Society guidelines use validated instruments, though the clock-drawing test has only been validated against the MMSE as a reference standard. Other tests in common use where there are no studies validating use in inpatient populations include the MOCA and the Addenbrooke's cognitive assessment revised version (ACE-R) (Mioshi et al., 2006). We contacted the authors of the MOCA, the Mini-Cog and the ACE-R who confirmed they knew of no validation studies specifically amongst older in-patients.

The prevalence of dementia in the studies varies from 6%-59%. This may reflect the changing demographics of acute hospital admissions over time, but must also reflect varying patient selection in the studies included. A carefully conducted and influential recent study (Sampson et al., 2009) reported prevalence of dementia among unselected older medical admissions at the higher end of this range.

In some of the studies the sample population was mixed with outpatients and on contacting the authors we were able to extract data from one study (O'Keeffe et al., 2011). The AMTS was the only instrument which had more than a single study examining its properties. We note that at a cut-off of  $<7$ , that across the three hospital inpatient samples reported, very similar sensitivities and specificities were found, although a cut off of  $<8$  is considered more usual in clinical practice. According to our meta-analysis it demonstrates good properties for a screening instrument, with good sensitivity and specificity ( $>0.8$ ), a diagnostic odds ratio of

greater than 20, and a positive and negative likelihood ratio of greater than 5 and less than 0.3 respectively. These LR cut offs are what is considered an accurate test, and the DOR cut off suggests the instrument is useful in clinical practice. The AUC value of 0.87 is also considered good.

The AMTS has practical limitations. The long term memory question (When did the first world war end?) is culturally specific and the recognition question requires two people to be at the bed space during the assessment. It does not require pen or paper so is suitable for people with visual or physical impairment. It is also brief, taking 3-4 minutes. Compared with MMSE, it is shorter, has been validated in more general hospital studies, and shows superior specificity (fewer false negatives). It is also freely available for use without copyright restrictions, as opposed to the MMSE. Used in a general hospital with 1000 beds, and 10,000 non-elective admissions of people over 65 years per year, assuming all screened and 40% prevalence for dementia, 4200 (42%) would screen positive, 3240 (32.4%) would be true positives and 960 (9.6%) false positives. Of the true positives, 1620 (16.2%) would be already known to services, and 1620 (16.2%) would then require further assessment. Therefore a total of 2580 further assessments would be needed. Assuming 60 minutes each per assessment, either in hospital or after discharge, this would lead to considerable increased resource implications, as well as the false positive patients (960) having potentially stressful assessments.

Our review has limitations. These include publication bias, whereby some studies that may show poor performance of our selected instruments may not have been published. Selection bias can also be a problem in meta-analysis, but we have minimised this by having a strict protocol and solving selection disagreements by consensus. Even using a gold standard reference criteria the prevalence of dementia can vary widely depending on the diagnostic

criteria used (Erkinjuntti et al., 1997), for example DSM IIIR and DSM IV, and this makes combining the data a challenge. The exclusion of non-English language studies also has potential for bias.

If screening is chosen, timing matters. Inpatient screening needs to take place after the initial acute illness has improved and a diagnosis of delirium has been excluded. As with any brief screen, a second stage procedure is always needed. Such a second stage would involve broadening assessments beyond cognitive tests. Ultimately, screening for dementia always has to be followed by a detailed expert assessment before diagnosis. In many cases such assessment may only be realistic after the hospital admission; screening identifies those warranting such detailed assessment.

At present, evidence that screening for dementia is effective is lacking (Brunet et al., 2012). If screening is chosen, instruments used need to be short, valid, reliable, acceptable and show good sensitivity and specificity. Given the high prevalence of dementia in hospitals then any screening instrument used must have been validated appropriately in this specific setting, as opposed to using tools validated in community settings where prevalence rates are much lower (Slater and Young, 2013). Few instruments have been researched in this setting, and further research is clearly needed, but available data should at least allow some predictions about impacts on service of systematic screening. Assuming a prevalence of 40% then any future validation study would need to recruit 154 patients (61 with prevalent dementia) for a study to be powered to 95% confidence +/- 10% (Guyatt, 2005). Any future research should explicitly report timing of screening during an admission, and to minimize bias should ideally ensure rater blindness between the index test and the gold standard test.



## 4.5 Conclusion

Many instruments are recommended for screening for dementia. A small number have been validated in general hospital inpatients. The AMTS, a fast and commonly used screening test, is currently the most researched instrument for this population, but the review is unable to recommend a single best instrument. There is a clear need for more robust evidence to best inform screening for dementia in hospital inpatients

### Key Points:

- Numerous tools are advocated to detect dementia and cognitive impairment
- Dementia is common and underdiagnosed in the hospital setting, so an admission is a potential opportunity to detect dementia
- Six discreet instruments have established properties in screening for dementia in hospital inpatients and only one, the AMTS, in more than one report
- Available data allows prediction of service and patient impacts of any screen for dementia amongst older inpatients
- There is a clear need for robust validation studies of dementia screening instruments in hospital inpatients

## 5 Diagnostic test accuracy of informant based tools to diagnose dementia in older hospital patients with delirium

### 5.1 Introduction

The previous chapter has demonstrated that there is a clinically significant degree of undiagnosed dementia and MCI in a cohort of older patients with delirium. Therefore, older patients with delirium are a target population to improve identification of dementia within the general hospital. However, pragmatic methods to identify dementia in patients with delirium do not currently exist. In chapter 4 it was shown that screening tools do exist to identify dementia in general hospital, but none of these have included patients with delirium. As delirium, by definition, is associated with an acute cognitive change from baseline, novel strategies to identify dementia in delirium are required. Informant based screening tools with relatives and carers, rather than performance based tools used directly with patients, may offer a solution.

This chapter will determine if two informant questionnaires offer a pragmatic method to identify dementia and MCI in patients presenting with delirium.

### 5.2 Methods

#### 5.2.1 Recruitment

Patients were recruited as described in section 2.1. Briefly, patients aged 70 years and over with an unplanned medical admission to a UK teaching hospital between March 2013 and November 2014 were screened for delirium. The screening used the Confusion Assessment

Method (CAM) (Inouye et al., 1990), Abbreviated Mental Test Score (AMTS) (Hodkinson, 1972), the Digit Span test, and a detailed review of the medical notes. If participants met the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV-TR) criteria for delirium (American Psychiatric Association, 2000) they were eligible for the study. Potential participants who were unable to communicate because of severe sensory impairment or non-competence in English were excluded, as were those deemed to be at risk of imminent death.

Patients with delirium were then invited to participate. Informed consent was sought from the potential participant if they had the mental capacity to give it. Otherwise, in accordance with the provisions of the Mental Capacity Act with respect to participation in research, the next of kin was consulted. They were also approached to act themselves as informants in the study. Informed consent was then gained from the informants.

An informant interview was then completed. This enquired about previous diagnosis of dementia or cognitive impairment and prior cognitive and physical function. The Informant was then asked to complete two rating scales, the short form of the Informant Questionnaire of Cognitive Decline in the Elderly (IQCODE-SF) (Jorm, 1994) and the 'AD8: The Washington University Dementia Screening Test', also referred to as the Eight-item Interview to Differentiate Aging and Dementia (AD8) (Galvin et al., 2005). The scales as used in the study are available as appendix. The informant was shown the scales, and instructions were given. They were then completed in private and placed in a sealed envelope to ensure appropriate blinding.

### 5.2.2 Informant tools

The informant tools are described in detail in section 2.1.5. In brief, the IQCODE-SF asks the informant to rate changes in cognition, memory and behaviours over a 10-year period. It has been validated in both primary care settings (Harrison et al., 2014), community settings (Quinn et al., 2014) and secondary care settings (Harrison et al., 2015) to diagnose dementia. It takes about 10 minutes for the informant to complete. The IQCODE-SF consists of 16 items that are rated one to five on an ordinal scale. The average rating of each item is calculated. Results range from one to five, where higher scores indicate a greater degree of cognitive impairment. The introductory wording was changed to ‘Now we want you to remember what your friend or relative was like 10 years ago and to compare it with what he/she was like *before they got the illness that brought them to hospital*’

The AD8 is a shorter screening informant interview, asking the informant to rate memory and thinking changes over a few years, rating eight items either yes, no or don’t know. It takes five minutes to complete and has been found to be sensitive and specific to dementia in a memory clinic population (Galvin et al., 2007b). The test is scored from zero to a maximum of eight, where higher scores indicate a greater degree of cognitive impairment.

### 5.2.3 Reference Standard

The reference standard diagnosis of dementia or MCI was made at an assessment 3 months after admission in survivors. This is described in detail in section 2.1.9. Briefly, the presence of persistent delirium was first established using DSM-IV-TR criteria for delirium. If no delirium was present a standardised history and examination, including the Addenbrooke’s Cognitive Examination III (ACEIII) (Hsieh et al., 2013) was performed to establish the presence or absence of dementia or mild cognitive impairment before the onset of the

delirium. Dementia and subtype was diagnosed using the DSM-IV criteria (American Psychiatric Association, 1994): (1) the development of multiple cognitive deficits, including memory impairment, and (2) the impairment is sufficiently severe to cause impairment in occupational or social function. MCI was diagnosed using current consensus diagnosis (Winblad et al., 2004): (1) the person is neither normal nor demented, (2) there is evidence of cognitive decline, and (3) that activities of daily living are preserved and complex instrumental functions are either intact or minimally impaired. To make the diagnosis of dementia or MCI at the index admission the symptoms of cognitive decline had to have been present for at least 6 months prior to the admission with delirium. All assessments were carried out by the author.

#### 5.2.4 Power calculations and statistical analysis

To evaluate the diagnostic accuracy of the IQCODE-SF and AD8 against a gold standard reference diagnosis the sample size was calculated at 124. This was based on the method recommended by Guyatt et al (Guyatt, 2005) and is described in more detail in section 2.3.

Receiver operating characteristic curves were generated for both tests and a calculation of the area under the curve (AUROC) made. These were made for a diagnosis of dementia and a diagnosis of combined cognitive impairment. Combined cognitive impairment is defined as dementia or MCI. Further analysis was undertaken on a subgroup of participants who had no recognised diagnosis of dementia on admission.

Sensitivity, specificity, the positive likelihood ratio (LR+), and the negative likelihood ratio (LR-) were calculated from the best cut-offs. In evaluating the relative misclassification costs in this population selected cut-offs that minimized false positive diagnoses were chosen. This reduces the burden of potentially stressful and unnecessary further investigation. Likelihood

ratios are a measurement of diagnostic accuracy and say how likely a person with a condition is to have a positive test (LR+) or a person without the condition is to have a positive test (LR-). Data were analysed using IBM SPSS version 20 for Windows. P values <0.05 were considered significant.

The chapter is reported using the Standards for Reporting of Diagnostic Accuracy (STARD) statement (Bossuyt et al., 2003).

## 5.3 Results

1327 older people admitted to hospital were screened for delirium and delirium was diagnosed in 228 (17.2%). 125 of 228 (54.8%) were recruited. The main reason for non-recruitment was the lack of an available consultee or informant (57/228, 25%). 22/228 (10%) were deemed at risk of imminent death, 15/228 (7%) were not competent in English, the consultee declined participation in 2/228 (1%) and 7/228 (3%) had been previously recruited.

Of the 125 recruited, 77 (62%) had a full assessment for the reference standard diagnosis. 25/125 (20%) had died, 10/125 (8%) declined the follow-up visit, 8/125 (6%) were not contactable for an assessment, and 5/125 (4%) had persistent delirium at assessment. There was no difference in age, gender or admission dementia status between those assessed for dementia at 3 months and those not. The mean age of the final sample assessed for reference criterion diagnosis of dementia was 84.4 and 69% were female. Participant flow through the study is illustrated as a flowchart in Figure 5-1.

At three month assessment 47/77 (61%) were diagnosed with dementia, 14/77 (18%) were diagnosed with MCI, and 16/77 (21%) had no cognitive impairment. Of those with dementia, this was newly diagnosed in 17/47 (36%).

In diagnosing DSM-IV dementia the AUROC curve for the IQCODE-SF was 0.93 (95% CI 0.86-1.00,  $p<0.0005$ ) and for the AD8 was 0.91 (95% CI 0.83-0.98,  $p<0.0005$ ). The selected cut-off of  $>3.82$  for the IQCODE-SF gave a sensitivity of 0.91, a specificity of 0.93, LR+ of 13.72 and a LR- of 0.09. The selected cut-off of  $>6$  for the AD8 gave a sensitivity of 0.83, a specificity of 0.90, a LR+ of 8.30 and a LR- of 0.19.

The traditional cut-off of the IQCODE-SF for diagnosing dementia in the general hospital (British Geriatric Society, 2005) is  $\geq 3.44$  for the IQCODE-SF. Using this cut-off in people with delirium gave greater sensitivity of 0.98 at the expense of lower specificity of 0.67.

In diagnosing combined cognitive impairment (DSM-IV dementia or MCI) the AUROC curve for the IQCODE-SF is 0.99 (95% CI 0.97-1.00,  $p<0.0005$ ) and for the AD8 is 0.97 (95% CI 0.93-1.00,  $p<0.0005$ ). The selected cut-off of  $>3.32$  for the IQCODE-SF gives a sensitivity of 0.93, a specificity of 0.93, LR+ of 14.9 and a LR- of 0.07. The selected cut-off of  $>3$  for the AD8 gives a sensitivity of 0.90, a specificity of 0.93, a LR+ of 14.4 and a LR- of 0.10.

47 participants had no previous recorded diagnosis of dementia or MCI on admission to hospital. This sub-group was also analysed. In diagnosing dementia the AUROC curve for the IQCODE-SF was 0.91 (95% CI 0.82-1.00,  $p<0.0005$ ) and for the AD8 was 0.83 (95% CI 0.71-0.96,  $p<0.0005$ ). The selected cut-off of  $>3.64$  for the IQCODE-SF gave a sensitivity of

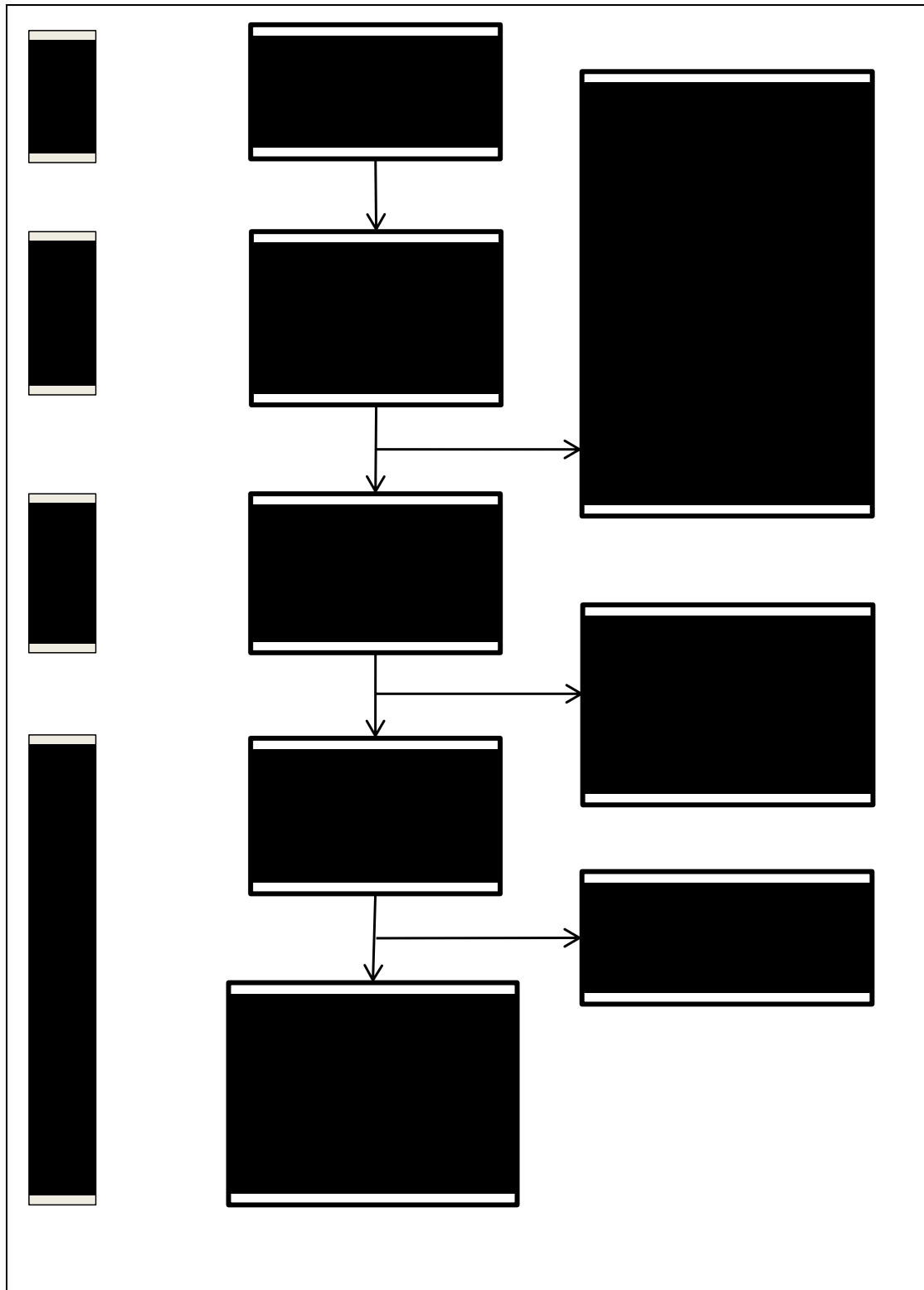
0.88, a specificity of 0.86, LR+ of 6.44 and a LR- of 0.12. The selected cut-off of  $>4$  for the AD8 gave a sensitivity of 0.77, a specificity of 0.86, a LR+ of 5.64 and a LR- of 0.25.

In diagnosing combined cognitive impairment (DSM-IV dementia or MCI) in participants with no previous recorded diagnosis of dementia or MCI the AUROC curve for the IQCODE-SF is 0.98 (95% CI 0.95-1.00,  $p<0.0005$ ) and for the AD8 is 0.94 (95% CI 0.88-1.00,  $p<0.0005$ ). The selected cut-off of  $>3.32$  for the IQCODE-SF gives a sensitivity of 0.87, a specificity of 0.93, LR+ of 13.93 and a LR- of 0.13. The selected cut-off of  $>3$  for the AD8 gives a sensitivity of 0.80, a specificity of 0.94, a LR+ of 12.9 and a LR- of 0.21.

There was no statistical difference between the AUROCs when comparing the performance of the IQCODE-SF and the AD8.

Table 5-1 shows sensitivity and specificity for various cut-offs with the recommended cut-off highlighted. Figure 5-2 and Figure 5-3 shows the ROC curves for the IQCODE-SF and AD8. Table 5-2 illustrates the diagnostic test accuracy values for the IQCODE-SF and AD8 including confidence intervals at the chosen cut-offs.



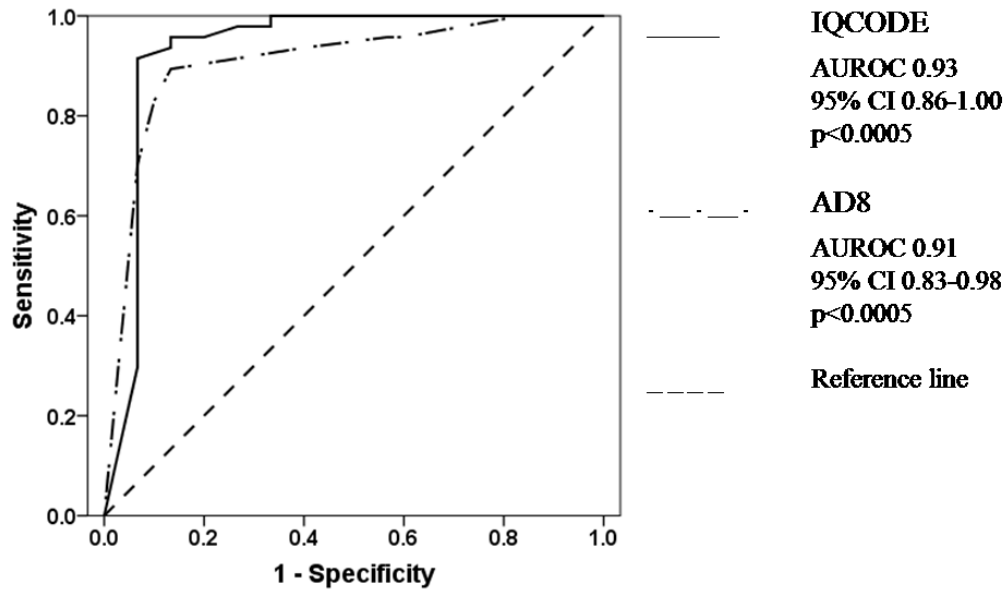


**Figure 5-1:** Flowchart showing participant flow through the study and derivation of final cohort.

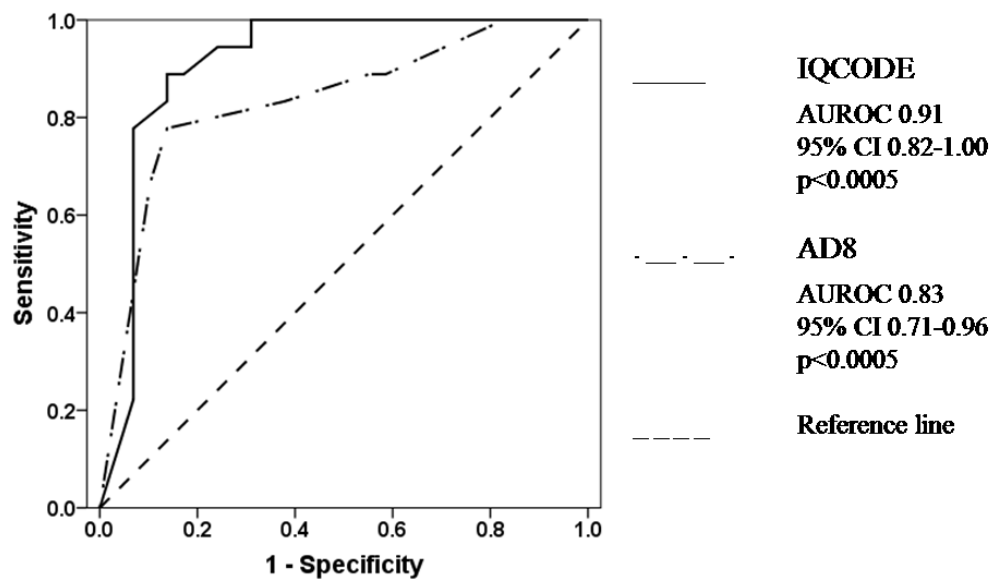
**Table 5-1: Sensitivity and specificity of the IQCODE-SF and AD8 at various cut-offs. Best cut-off highlighted in grey**

Dementia			
	Cut-off >	Sensitivity	Specificity
IQCODE-SF	3.59	0.96	0.80
	3.65	0.96	0.83
	3.715	0.96	0.87
	3.78	0.94	0.87
	3.82	0.92	0.93
	3.935	0.87	0.93
AD8	3	0.93	0.60
	4	0.89	0.87
	6	0.83	0.90
	7	0.70	0.93
Combined Cognitive impairment (Dementia or MCI)			
	Cut-off >	Sensitivity	Specificity
IQCODE-SF	3.34	0.93	0.94
	3.375	0.92	0.94
	3.41	0.90	0.94
	3.5	0.89	1.00
AD8	2	0.95	0.75
	3	0.90	0.94
	5	0.75	1.00

**2a ROC for all patients (N=77): Dementia**

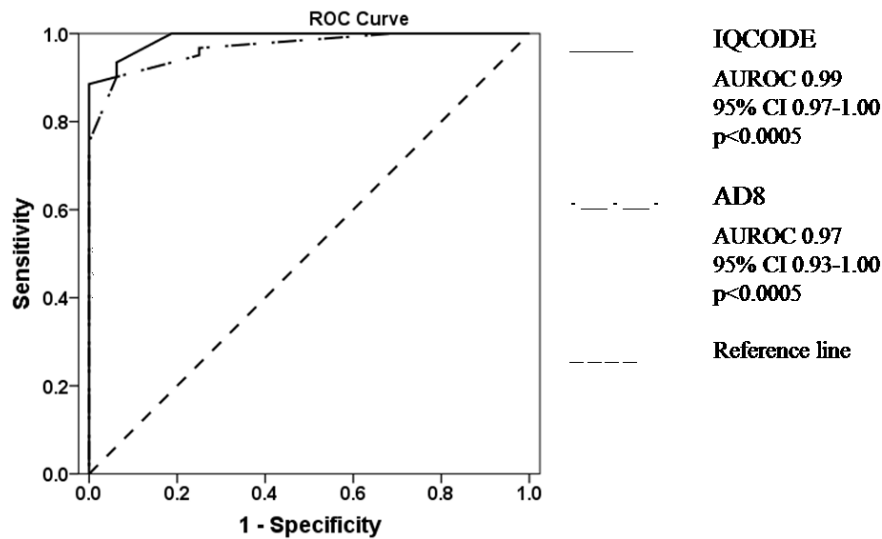


**2b ROC for patients with no recorded dementia (N=47)**

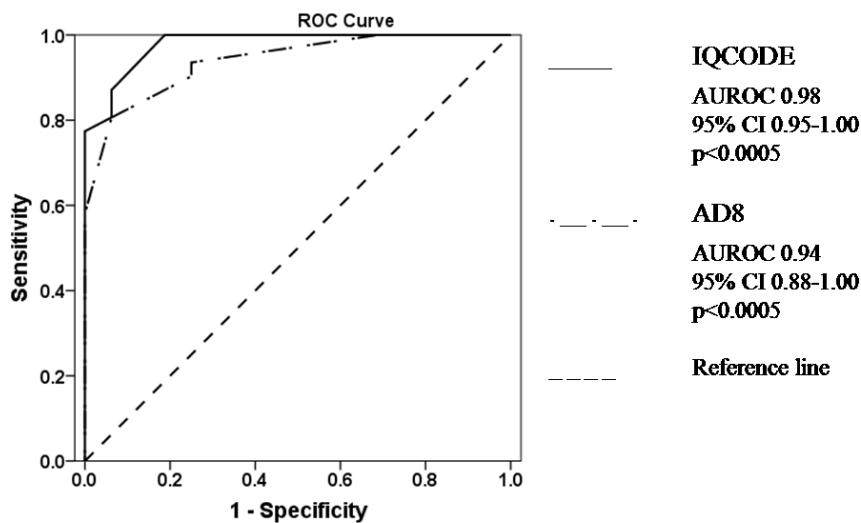


**Figure 5-2: Receiver operating characteristic curves for the IQCODE-SF and the AD8 to diagnose dementia in a) all patients and b) patients with no diagnosis of dementia or MCI on admission. AUROC = area under the receiver operating characteristic curve**

**3a** ROC for all patients (N=77): Combined cognitive impairment



**3b** ROC for patients with no recorded dementia (N=47): Combined cognitive impairment



**Figure 5-3: Receiver operating characteristic curves for the IQCODE-SF and the AD8 to diagnose combined cognitive impairment (dementia/MCI) in a) all patients and b) patients with no diagnosis of dementia or MCI on admission. AUROC = area under the receiver opera**

**Table 5-2: Table of diagnostic test accuracy of the IQCODE-SF and AD8 at set cut-offs.**

Reference Dx		Test/ cut off	Sen	Spec	LR+	LR-	PPV	NPV
Dementia	Whole cohort	IQCODE	0.91	0.93	13.72	0.09	0.96	0.88
		>3.87	(0.79-0.97)	(0.76-0.99)	(3.58-52.50)	(0.04-0.23)	(0.84-0.99)	(0.70-0.96)
		Prevalence 61%						
	No previous dementia Dx	AD8	0.83	0.90	8.30	0.19	0.92	0.77
		>7	(0.69-0.92)	(0.72-0.97)	(2.81-24.47)	(0.09-0.36)	(0.79-0.98)	(0.59-0.89)
		Prevalence 38%						
Dementia or MCI	Whole cohort	IQCODE	0.88	0.86	6.44	0.12	0.80	0.92
		>3.68	(0.64-0.98)	(0.67-0.95)	(2.56-16.24)	(0.05-0.48)	(0.56-0.93)	(0.74-0.99)
		Prevalence 79%						
	No previous dementia Dx	AD8	0.77	0.86	5.64	0.25	0.77	0.86
		>5	(0.52-0.95)	(0.67-0.95)	(2.19-14.47)	(0.11-0.62)	(0.52-0.92)	(0.67-0.95)
		Prevalence 66%						
Dementia or MCI	Whole cohort	IQCODE	0.93	0.93	14.9	0.07	0.98	0.78
		>3.34	(0.82-0.98)	(0.68-0.99)	(2.24-99.8)	(0.02-0.18)	(0.89-0.99)	(0.53-0.95)
		Prevalence 79%						
	No previous dementia Dx	AD8	0.90	0.93	14.4	0.10	0.98	0.71
		>4	(0.79-0.95)	(0.68-0.99)	(2.15-96.4)	(0.04-0.22)	(0.89-0.99)	(0.47-0.87)
		Prevalence 66%						
Dementia or MCI	Whole cohort	IQCODE	0.87	0.93	13.93	0.13	0.96	0.79
		>3.34	(0.69-0.96)	(0.68-0.99)	(2.07-93.4)	(0.06-0.34)	(0.80-0.99)	(0.53-0.95)
		Prevalence 79%						
	No previous dementia Dx	AD8	0.80	0.94	12.9	0.21	0.96	0.71
		>4	(0.61-0.91)	(0.68-0.99)	(1.92-86.7)	(0.10-0.43)	(0.78-0.99)	(0.47-0.87)
		Prevalence 66%						

Sen = sensitivity, spec = specificity, LR+ = positive likelihood ratio, LR- = negative likelihood ratio, PPV = positive likelihood ratio, NPV = negative likelihood ratio

## 5.4 Discussion

For the first time the diagnostic test accuracy of the IQCODE-SF and AD8 in diagnosing dementia and combined cognitive impairment in older people presenting with delirium has been presented. The IQCODE-SF and AD8 had excellent sensitivity, specificity and discriminatory ability in diagnosing both conditions. An AUROC of greater than 0.9 is considered excellent. To illustrate the IQCODE-SF at a cut-off of  $>3.82$  to diagnose dementia in 100 people with delirium would correctly identify 56 of the 61 with dementia and would falsely imply a diagnosis of dementia in 3 of the 39 without dementia. Interpreting the likelihood ratios of the IQCODE-SF at a cut-off of  $>3.82$  to diagnose dementia, a positive test is 13 times more likely to occur in someone with dementia rather than someone without dementia. A negative test is 0.07 times less likely to occur in someone with dementia rather than someone without. This indicates good discrimination after a test has been performed. A positive likelihood ratio of greater than 10 and a negative likelihood ratio of less than 0.1 indicates a test is useful (Jaeschke et al., 2002).

There were two points during the study where there was a risk of selection bias. Firstly, not all patients diagnosed with delirium were recruited. The main reason for this was the lack of an available consultee and/or informant. However, there were no gender or age differences between those recruited and those not. Those without an available consultee represent a significant number of those with delirium. Secondly, not all recruited participants were available for reference diagnosis assessment at 3 months. The main reason was mortality, with 25 (20%) having died prior to follow-up. This is in keeping with the expected mortality

of delirium (Siddiqi et al., 2006). It would also be reasonable to expect a higher mortality in those with dementia.

Because of the perceived difficulty with diagnosing dementia among patients in hospital with delirium, a strict reference criteria was applied and all assessments carried out by the trained author. The author was appropriately blinded to the index test result. Therefore, the findings are likely to be robust and representative of a real world general hospital. The study recruited to the appropriately powered sample size. The reported prevalence of delirium of 17.9% is similar to previous studies in acute admissions (Collins et al., 2010) indicating the screening was robust.

Neither the IQCODE-SF nor the AD8 have been previously validated to diagnose dementia or MCI in patients with delirium. One previous study, identified in chapter 4, has examined the diagnostic test accuracy of the IQCODE-SF to diagnose dementia in older hospital inpatients, excluding those with delirium. This reported a sensitivity of 1.00 and specificity of 0.86 for detecting DSM-III-R dementia at a cut-off of  $>3.44$  (Harwood et al., 1997). This study chose a lower cut-off of the IQCODE-SF in order to reduce false negatives, at the expense of false positives. However, they also report various cut-off points and at  $\geq 3.76$ , report sensitivity of 0.92 and specificity of 0.93 for the IQCODE-SF, which are very similar to the results reported here. A further difference is that the prevalence of dementia is much lower (10%) in this study. This is probably a reflection of the changing demographics, with more older people using hospital services and the subsequent increase in dementia prevalence within hospital populations. There are no previous studies examining the use of the IQCODE-SF or AD8 to detect MCI.

Although the IQCODE-SF has not been formally assessed in people with delirium, it is commonly used as a proxy for previous cognitive impairment in delirium research using different cut-offs. A cut-off of  $>3.30$  has been used in studies of intensive care unit delirium (Pisani et al., 2007) and a cut-off of  $>3.5$  in a general hospital population (O'Regan et al., 2014). The IQCODE-SF has also been reported to predict postoperative delirium in elective surgery patients (Priner et al., 2008). The AD8 has been reported to predict in-hospital delirium (Zeng et al., 2014) but has not previously been validated to recognise dementia in a hospital population.

Although both tests have similar diagnostic accuracy, both have advantages and disadvantages. The IQCODE-SF would appear to be slightly better when detecting dementia in those with no previous diagnosis (AUROC 0.91 vs 0.83), but the test accuracy is still very good and there is no statistical difference between the AUROC using IQCODE-SF or AD8. The AD8 is simpler and quicker to complete, however it has a higher number of false positives. The IQCODE-SF still only takes 10 minutes to complete and the extra detail gathered from the tool may be of clinical relevance. The IQCODE-SF has been translated into 14 languages. Both are freely available without cost (Australian National University, 2015, Knight Alzheimer's Disease Research Centre, 2015). Given this, it is difficult to recommend one test over the other. It would be the author's preference to recommend the IQCODE-SF as it provides better-detailed clinical information and has better specificity and positive likelihood ratios, so will result in fewer false positive results than the AD8.

Informant tools do have limitations. They rely on the availability of an informant and, particularly in the most vulnerable patients, an informant may not be available. Information collected from the informant to populate the scales may also be affected by recall bias.



Characteristics of the informant may influence the result such as depression or cognitive impairment. However, the strengths of informant tools are to negate problems with pre-existing educational background, culture or language difficulties.

The impact of the identification of MCI in hospitals has not been studied before. MCI should be seen as a condition of high risk, in that patients with MCI are at high risk of developing dementia. However, currently no intervention exists to delay or halt this conversion. It is also not known what impact MCI specifically has on hospital outcomes, but studies, including the Nottingham cohort study (see 1.2.2, Table 1-6) have measured the impact of 'cognitive impairment' which will include both dementia and MCI. Clearly future research to address specifically the impact of MCI on hospital stay is needed.

The findings are significant for the research community as the IQCODE-SF or AD8 can now be used to identify robustly prior dementia in studies of delirium cohorts at validated cut-offs.

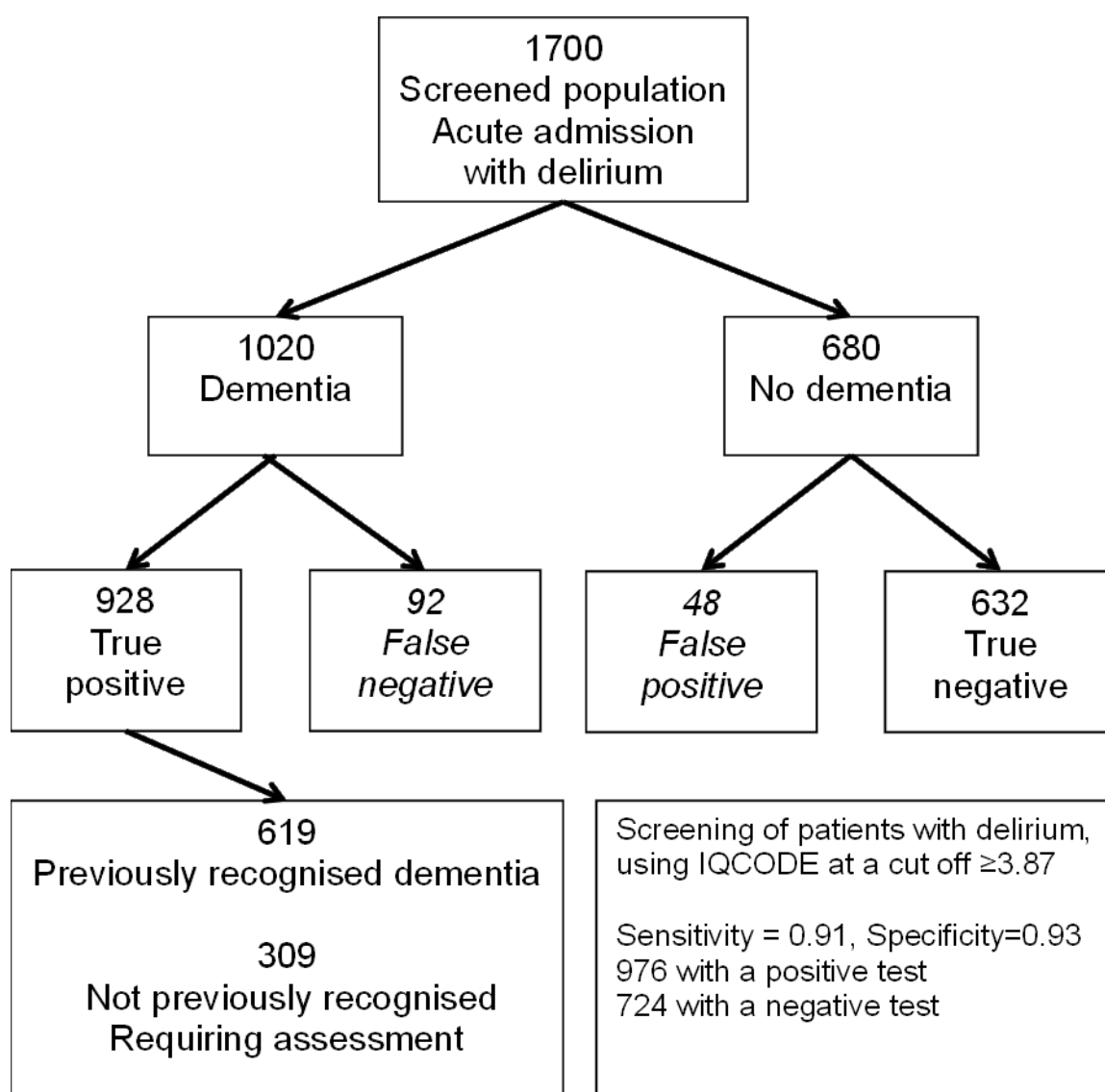
The findings also have a potentially significant impact on routine clinical practice, given the high prevalence of delirium and unrecognised dementia in the general hospital. Figure 5-4 is a flow chart extrapolating the diagnostic and prevalence data to a hypothetical acute hospital with 1000 beds and 10,000 non-elective admissions of older people yearly. It would be expected that 1700 (17%) would have delirium, with 60% of those also having dementia. Using the IQCODE-SF at  $>3.82$  to diagnose dementia; 928 (55%) would have a true positive result, with 309 having previously unrecognised dementia. 48 (3%) would have a false positive result, and potentially stressful unnecessary assessments. However, it would also allow the identification of an extra 309 patients in acute hospital with dementia, and the subsequent improvement in care that should bring. A timely diagnosis of dementia during hospital admission may ameliorate adverse events associated with a hospital stay (Mecocci et

al., 2005), allow signposting to a suitable cohort ward (Goldberg et al., 2013) or trigger the need for comprehensive geriatric assessment (Ellis et al., 2011). However, the case for early identification of dementia, or indeed MCI, as an intervention to reduce harm has not been made yet.

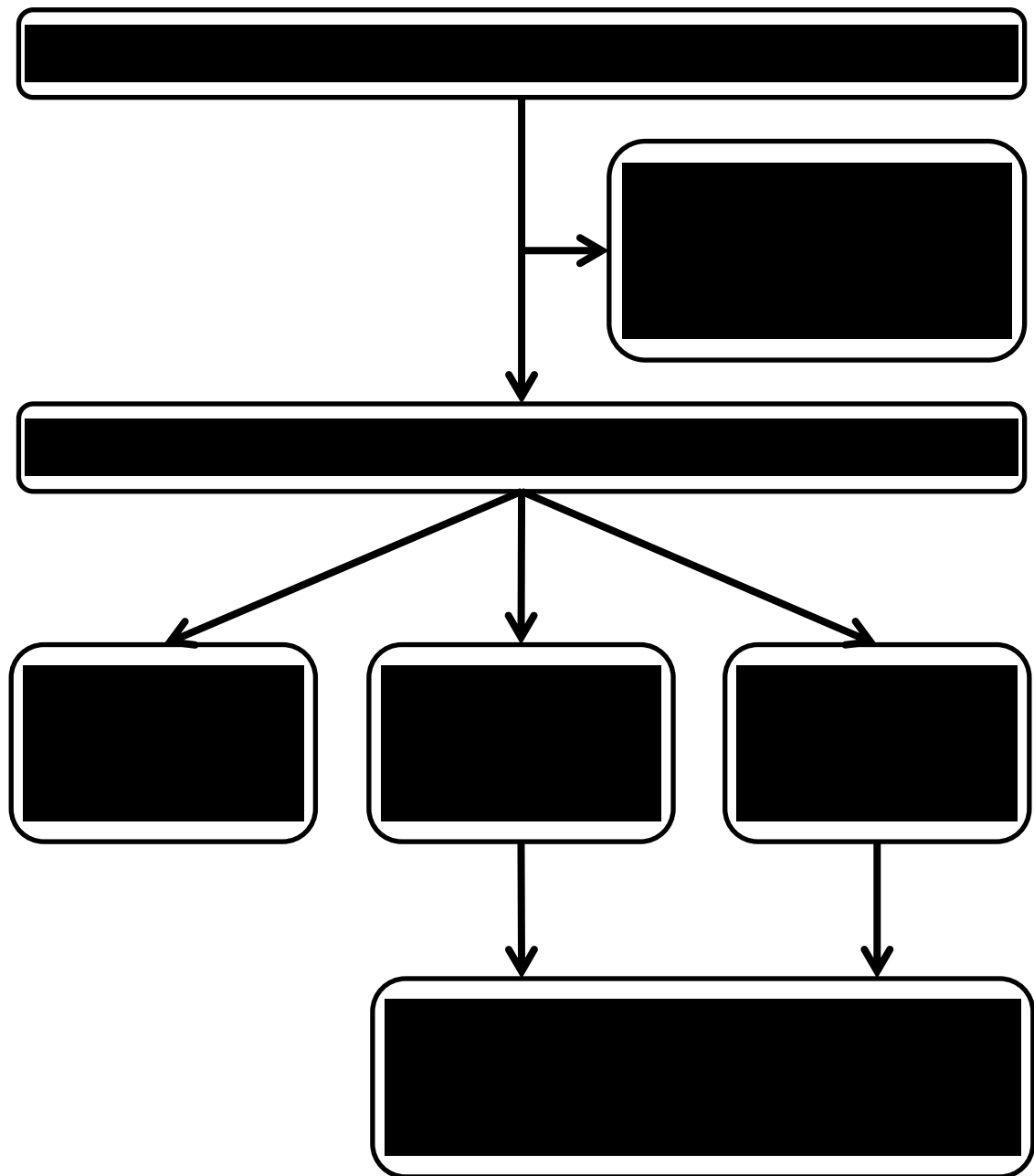
### *Suggested Clinical Guideline*

Given the findings in this chapter a suggested clinical algorithm is presented in Figure 5-5. On admission with delirium all patients should have an IQCODE-SF performed if an informant is available. At this interview, any previous diagnosis of dementia or MCI should be recorded. A score of  $<3.32$  ( $\leq 53/80$ ) suggests no evidence of MCI or dementia. A score of  $>3.32$  ( $\geq 54/80$ ) suggests either MCI or dementia, and a score of  $>3.82$  ( $\geq 62/80$ ) suggests dementia. Those with no previously recorded diagnosis should then be considered for detailed assessment of cognition and function on resolution of delirium. This could be pre-discharge or at 3 month follow-up.

To conclude, after demonstrating that there is a high proportion of undiagnosed combined cognitive impairment in older people with dementia in chapter 3, both the IQCODE-SF and AD8 have been demonstrated to be sensitive and specific tools to detect dementia and combined cognitive impairment in older people presenting to hospital with delirium. They are simple and quick to administer as well as being freely available. Given the high prevalence of delirium in older people in hospital, the routine use of either tool in practice will have important clinical impact, potentially improving the recognition of dementia as well as the care of this vulnerable population.



**Figure 5-4: Flow chart illustrating the use of the IQCODE-SF for screening patients with delirium for dementia in a hypothetical 1,000 bedded hospital**



**Figure 5-5: Proposed diagnostic flowchart for using the IQCODE-SF in patients presenting to hospital with delirium. MCI = mild cognitive impairment**

## 6 Predicting outcome in older hospital patients with delirium: A systematic literature review

The objective of the following systematic review is to report which predictors of adverse outcome in delirium have been reported in the literature. The second readers were Dr Daisy Wilson of the University of Birmingham, Dr Sarah Richardson of the University of Newcastle and Professor Janet Lord of the University of Birmingham. The author devised the protocol and planned the organisation of the review. All readers contributed to reviewing articles, data extraction and contributed to data analysis. The following is exactly as published in the International Journal of Geriatric Psychiatry (2015, Aug 24, doi: 10.1002/gps.4344.[Epub ahead of print]) except for some minor formatting changes.

### 6.1 Introduction

Delirium is a serious and common syndrome affecting mainly older people(Inouye et al., 2014). It is an acute neuropsychiatric condition affecting global cognitive function, typically attention and working memory, as well as consciousness. Delirium is often undiagnosed, yet affects between 14-24% of hospital admissions and develops in between 29-64% of patients on general medical and geriatric medicine wards (Inouye et al., 2014). The clinical presentation of patients with delirium is varied and specific motor sub-types, hyperactive and hypoactive, have been described (Inouye et al., 2014).

Delirium is associated with adverse clinical outcomes including increased mortality, increased length of hospital stay, more hospital-acquired complications, such as falls and pressure sores, and increased rates of institutionalisation, re-admission and dementia (Siddiqi et al., 2006,

Witlox et al., 2010). These outcomes have significant morbidity both for the patient and their carers, causing considerable short and long-term distress (Partridge et al., 2013). They also lead to additional healthcare costs, estimated at an extra £13,000 per admission (Akunne et al., 2012).

In studies of older people in general, it has been possible to identify predictors of poor outcomes such as death, increased length of stay, reduced function and institutionalisation (Drame et al., 2008, Campbell et al., 2004). Identifying predictors of poor outcomes specific to delirium would allow clinicians to risk stratify patients in order to focus immediate and follow-up management strategies according to baseline risk with the aim of improving outcomes. Exploration of the factors behind the heterogeneity of delirium presentation and outcome may also inform future research into its pathophysiology and treatment.

## 6.2 Objectives

To identify published predictors of poor outcome in hospitalised patients with delirium.

## 6.3 Method, Search Criteria and Strategy

We undertook a comprehensive literature review of the following databases: MEDLINE, Embase and PsycINFO. The primary search terms were delirium, acute confusional state and confusion. These were searched for together with recognised terms for prognosis, mortality and outcomes (Wilczynski et al., 2004). The full search strategy is given in appendix 3. The databases were accessed on 02/11/14 and databases searched from 1980 onwards. Abstracts were reviewed to determine which papers to extract by two reviewers (TJ + DW). Inclusion criteria at that stage were studies that evaluated variables with recognised outcomes in

patients with delirium. A further search of the references of selected papers was completed to find additional papers. A forward citation search of selected papers was also carried out.

The studies selected by these processes were obtained in full and reviewed independently by three reviewers (TJ, DW, and SR) against the following inclusion criteria:

1. Included patients with delirium, diagnosed using a recognised and validated method
2. Included clearly defined outcomes; death, institutionalisation, length of stay and cognitive change;
3. Variables used as predictors were clearly defined with appropriate statistical analysis.
4. Included patients in the general hospital, rehabilitation facilities or care homes, but not in the intensive care setting or community;

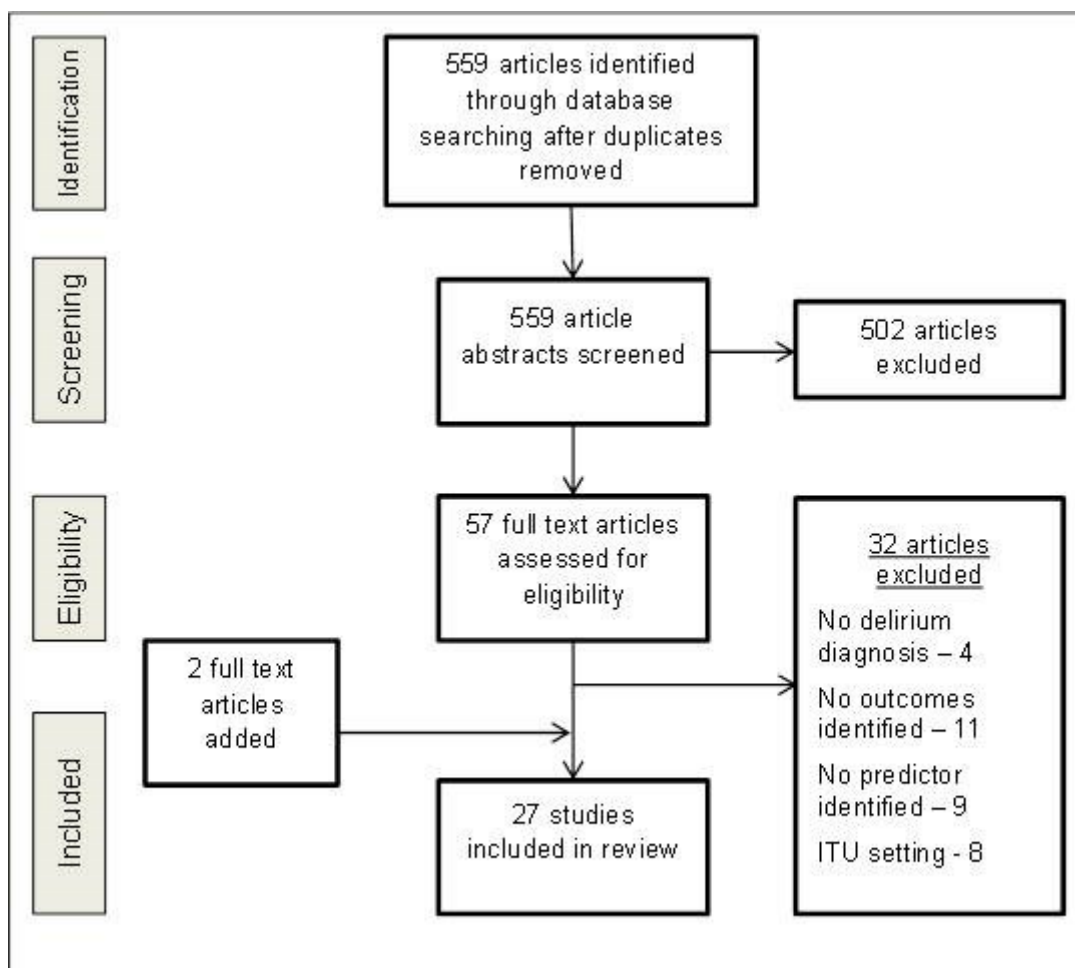
Exclusion criteria were non-English language papers and non-human studies.

Once included, the following information was recorded on a standardised proforma: reference, setting, study group size, diagnostic tool, outcomes, covariates used, predictors identified with associated hazard ratio (HR) or odds ratio (OR) if quoted. The included studies were reviewed by a fourth reviewer (JL) who also discussed any disagreement on inclusion.

We used the Newcastle-Ottawa Quality Assessment Scale (Wells et al., 2012) to assess selected studies for risk of bias. We followed the Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies (MOOSE) when reporting findings (Stroup et al., 2000).

## 6.4 Results

The initial search returned 843 articles of which 88 were not in English. Fifty-seven articles were selected having met the criteria. Two further articles were identified from the reference lists of selected articles. Of those 59, 27 met the inclusion criteria. No further studies were identified by a forward citation search. Figure 6-1 illustrates the study selection. The individual studies with relevant extracted data and Newcastle-Ottawa scores (NOS) are available in appendix 3 (supplementary tables 2 and 3). NOS scores ranged from six to nine (maximum nine) suggesting a low risk of bias across all studies selected.



**Figure 6-1: Flow chart of study selection**



## **Patients**

Mean age of participants ranged from 70 to 89 years and the majority of studies included more women than men.

## **Setting**

Thirteen studies were set in acute and general medical admission wards, six in hip fracture patients, four in post-acute and rehabilitation units, two in palliative care units and a single study in the emergency department. Ten studies were based in the United States of America, four in Canada, three in Italy, two in the United Kingdom, two in Finland, two in Ireland and a single study was based in Chile, South Korea, Netherlands and Taiwan.

## **Diagnosis of delirium**

To diagnose delirium, eight studies used the gold standard of the Diagnostic and Statistical Manual of Mental Disorders (DSM), and 19 used the Confusion Assessment Method (CAM)

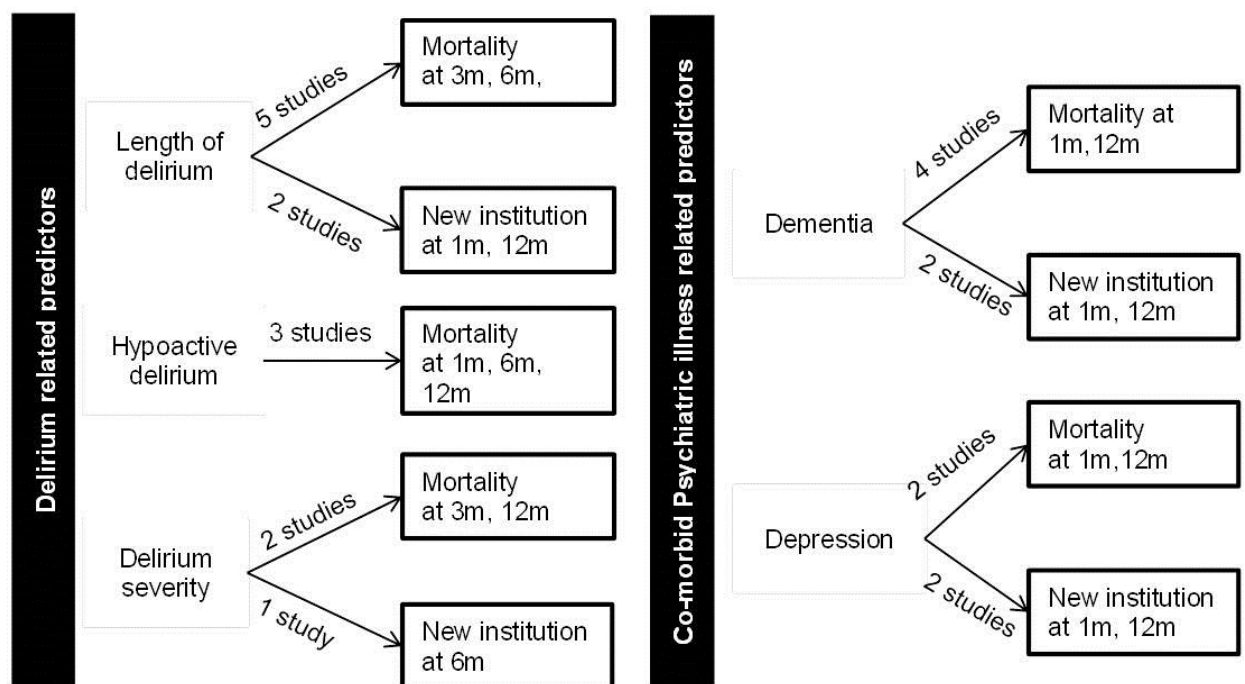
## **Outcomes**

In the 27 studies, mortality as an outcome was described 25 times (outcome mortality ranged from one month to 40 months), new institutionalisation five times, length of hospital stay once and a single study used a combined outcome of death, new institutionalisation or functional decline. There were no studies describing cognitive outcomes.

### **6.4.1 Predictors of poor outcomes**

In the 27 studies, eighteen main predictors of these outcomes are described.

Four broad themes were identified when analysing the predictors identified; delirium related predictors, co-morbid psychiatric illness related predictors, patient related predictors, and biomarker related predictors. Figure 6-2 illustrates the five most frequently reported predictors.



**Figure 6-2: Flowchart of the most frequently reported predictors and the reported outcomes. The number of studies reporting the predictor and outcome is represented on the arrow. New institution = new institutionalisation**

#### 6.4.1.1 Delirium related predictors

##### *Motor subtype*

Seven studies (N=1260 with delirium) examined the effect of motor subtype of delirium on outcomes. Three studies suggest the hypoactive subtype has worse outcome, with association with mortality being shown in a palliative care population (Meagher et al., 2011). Two

studies in a post-acute care facility showed a HR for mortality over 12 months of 1.62 (95%CI 1.11-2.37) for hypoactive delirium (Kiely et al., 2007) and a HR of 3.98 (95% CI 1.76-8.98) for mortality over six months in patients with hypoactive delirium and dementia (Yang et al., 2009) when compared with patients with hyperactive delirium. In a hip fracture population, hyperactive delirium was associated with a six fold (OR 5.9 95% CI 1.3-29.0) increased risk of mortality or new nursing home placement (Marcantonio et al., 2002). However, three studies demonstrated no relationship between motor subtype and outcomes (DeCrane et al., 2011, Slor et al., 2013, Kelly et al., 2001).

### *Duration*

The prognostic importance of the duration of delirium was examined in eight studies (n=871 with delirium). Every day of delirium was associated with a HR of 1.17 (95% CI 1.07-1.28) for death over a six month period (Bellelli et al., 2014a), and delirium longer than 48 hours carried a HR of 1.16 for mortality over three months, in comparison to the population whose delirium resolved within that period (Gonzalez et al., 2009). Persistent delirium at discharge was associated with greater mortality or new nursing home placement at twelve months (McAvay et al., 2006), and persistent delirium at six months had a HR of 2.9 (95% CI 1.9-4.4) for mortality over the subsequent six months (Kiely et al., 2009). In a hip fracture group, persistent delirium at one month was associated with mortality, new nursing home placement and reduced functional outcomes at six months (Marcantonio et al., 2000). Conversely, in a hip fracture population prolonged delirium (lasting greater than four weeks) was not associated with worse outcomes (Lee et al., 2011) and recovery from delirium was not associated with length of stay (Adamis et al., 2006)

### *Delirium severity*

In three studies (N=465 with delirium), severity of delirium was assessed using the Memorial Delirium Assessment Scale (MDAS). A rise by two points on the scale was associated with an OR of 1.16 (95% CI 1.06-1.26) of poor outcome (Dasgupta and Brymer, 2014), an MDAS score of greater than 24 was associated with increased mortality at 3 months (Kelly et al., 2001), and an MDAS of greater than 12.44 was associated with a relative risk (RR) of 3.1 (95% CI 1.2-8.2) for nursing home placement at six months in a hip fracture population (Marcantonio et al., 2002). Caution is warranted here given the classifications of severe delirium using different MDAS scores.

#### *Missed diagnosis*

Missed diagnosis of delirium in an emergency department population had a HR of 8.22 (95% CI 1.69-39.98) for mortality at six months (N=107 with delirium), opposed to a non-significant HR of 5.63 (95% CI 0.53–19.09) in a diagnosed group (Kakuma et al., 2003). However, caution is needed when interpreting this study given the low numbers of actual deaths in this group, leading to wide confidence intervals.

#### 6.4.1.2 Co-morbid psychiatric illness as predictors

The association of delirium with other psychiatric illness was investigated in six studies (N=789 with delirium). Three studies showed that co-morbid dementia was associated with worse outcomes. In medical patients a diagnosis of delirium alone carried a HR of death at 12 months of 1.6 (95% CI 1.06-1.26), but in patients with delirium and dementia this was increased to a HR of 2.3 (95% CI 1.1-5.5) (Bellelli et al., 2007). Delirium superimposed on dementia (DSD) was associated with increased mortality and new institutionalisation at one month (Givens et al., 2008) and one year (Morandi et al., 2014). Conversely, a single study

showed prior cognitive impairment or dementia was protective for mortality at one year (McCusker et al., 2002).

In a general medical cohort, delirium with depression was associated with a HR for death or new nursing home placement at 1 month of 5.38 (Givens et al., 2009). The cumulative addition of dementia and/or depression superimposed with delirium was associated with an increasing adjusted OR of 3.90 for death or new nursing home placement at 1 month (Givens et al., 2008).

#### 6.4.1.3 Patient related predictors

Patient related predictors of poor outcome were investigated in five studies (N=1073 with delirium). Increased age predicted worse outcomes in three studies (Dasgupta and Brymer, 2014, Tsai et al., 2012, Leonard et al., 2008) and frailty (defined as a frailty index of >0.25) was associated with shorter survival times in a cohort of medical patients with delirium (Eeles et al., 2012). The presence of organ failure and lower initial cognitive test score was associated with shorter survival times (Leonard et al., 2008) as was anaesthetic risk score (Morandi et al., 2014). Hypoxia, acute kidney injury and worse baseline function were associated with poor recovery at 3 months (Dasgupta and Brymer, 2014). However, these factors are also known predictors of outcome in all older patients, so these studies may simply represent the underlying illness severity rather than a factor of the delirium itself.

#### 6.4.1.4 Biomarkers as predictors

Biomarkers as predictors of poor outcome were investigated in three studies (N=126 with delirium). A set of cerebrospinal fluid (CSF) studies performed in delirium patients showed that raised cerebrospinal fluid (CSF) 5-Hydroxyindoleacetic acid (5-HIAA)(Koponen et al., 1994a) and reduced CSF acetylcholinesterase activity were associated with reduced time to

death over a four year period (Koponen et al., 1994b). Reduced albumin was associated with increased 6-month mortality (Bellelli et al., 2014a)

Figure 6-3 shows each outcome grouped with each predictor identified:

Outcome		Predictors identified, in order of frequency
Mortality	1 month	Hypoactive subtype, length of delirium, delirium and depression
	1-6 months	Hypoactive subtype, severity of delirium, dementia, length of delirium, hyperactive subtype, age, ↓serum Alb, missed diagnosis
	=>1 year	Length of delirium, hypoactive subtype, dementia, no dementia, illness severity, age, hospital length of stay
	Reduced survival time	Length of delirium, frailty, age, ↑CSF 5-HIAA, ↑CSF AcHE activity
New Institutionalisation		Persistent delirium, delirium and depression, delirium severity, hyperactive subtype

**Figure 6-3: Outcomes listed with associated predictors identified**

We did not attempt meta-analysis of the selected study outcomes due to the heterogeneity of the studies in terms of populations, statistical methods used and varied outcome measures.

## 6.5 Discussion

Nine predictors of clinically important outcomes in patients with delirium have been identified from 27 studies. The main predictors in patients with delirium were across four

broad themes. The most frequently reported predictors were increased duration of delirium, the hypoactive subtype, delirium severity assessed by MDAS, and co-morbid dementia and depression.

A limitation of this review is publication bias, whereby some studies that may show negative results have not been published. Selection bias in the systematic review process has been minimised by having a strict protocol and solving selection disagreements by consensus. The exclusion of non-English language studies also has potential for bias, but the number of abstracts excluded was relatively low. The selected studies themselves all had a low risk of bias when assessed using the Newcastle-Ottawa Scale (NOS). However, 10 of the 27 studies were at risk of bias when assessed for comparability by the NOS indicating that appropriate controlling for known confounders was not done.

There was some differences in how delirium was defined and diagnosed, with the majority of studies using the CAM, based on criteria taken from the DSM-III. A true reference criterion, for example DSM-IV or ICD-10, was used in eight studies. The duration of delirium is an important predictor. An explanation for this observation may be that the stimulus causing the delirium is more severe or prolonged, but it may also be due to impaired negative feedback from the stress response, thus causing on-going inflammatory brain pathology; a reduced ‘switch off’. This is hypothesised to occur in older brains with pre-existing neuropathology (MacLullich et al., 2008).

Hypoactive delirium is also associated with poor outcomes. Hypoactive delirium is more commonly missed as a diagnosis than in hyperactive patients so a delay in recognition and treatment may be a cause for this (Inouye et al., 2001). However, given the heterogeneity of delirium phenomenology, it may be that hypoactive patients have a more severe global

pathology, akin to severe illness behaviour. This in turn may lead to a risk of increased complications of inactivity, including dehydration, pressure damage, hypoventilation and venous thrombosis.

The relationship between dementia and delirium outcomes is conflicting. Delirium is more common in people with dementia and this is thought to be due to pre-existing neuropathology causing the brain to be at higher risk, mainly through an increase in a 'primed' microglial population (Cunningham, 2013). Microglia are the principal macrophage population in the brain and have an important role in initiating and managing the inflammatory cascade in response to a peripheral or direct brain insult. The poorer outcomes seen may be representative of this underlying pathology, and it is also important to note that delirium itself would appear to worsen cognitive decline in those both with and without pre-existing dementia (Davis et al., 2012). A single study demonstrates dementia as protective, and this may be an illustration of a less severe systemic insult being required to cause a delirium in dementia patients. In this case the insult is more benign and thus the outcomes better. As dementia itself is a risk factor for poor long term outcome a study which adjusts for both illness severity and baseline cognition would be of help.

Other potential confounders in observational studies of delirium include the disease severity of the underlying precipitant that prompted the episode of delirium, as well as the complex co-morbidity and frailty of patients who are at higher risk of developing delirium. Although most studies attempted to correct for these using recognised scales, these are still difficult to control for reliably.

The use of biomarkers for prediction of outcome is less well researched. A set of data on CSF biomarkers is interesting, suggesting a role for serotonin in the pathophysiology of delirium,



as well as confirming previous views about acetylcholine being a primary neurotransmitter in the development of delirium (Hsieh et al., 2008). Although not necessarily practical in routine clinical practice, studies of this kind provide an important insight into the neuropathological mechanisms underlying delirium and as such, further work is justified

## 6.6 Conclusions

In conclusion, a number of important predictors of poor outcomes in patients with delirium have been demonstrated. The most numerous described and clinically important would appear to be the duration of the delirium episode, delirium severity, a hypoactive motor subtype and pre-existing psychiatric morbidity with dementia or depression. In general, these are easily recordable variables which could be used in clinical practice to focus direct management and guide discussions regarding prognosis. The review has also further demonstrated the broad clinical phenotype of delirium seen in practice.

## 7 Clinical and biological predictors of adverse outcome and mortality in older patients with delirium

### 7.1 Introduction

The previous chapter reported a number of important predictors of adverse outcome in patients with delirium from existing literature. The most commonly reported were delirium duration, the hypoactive subtype of delirium, delirium severity and co-existing dementia. These predictors were mainly identified in studies comparing outcomes between patients with and without delirium, with only six of the 27 identified studies setting out to evaluate predictors of adverse outcome prospectively. Only one of the six was based in acute medical inpatients (McCusker et al., 2002).

This chapter sets out results of a study addressing the third key thesis question which is: among older people with delirium and dementia in a general hospital, which clinical and biochemical features are associated with adverse outcomes? Therefore the aims of the chapter are to report whether any of the following are associated with adverse outcomes (increased length of stay, new institutionalisation, and death): (a) key clinical factors (duration of delirium, severity of delirium, delirium subtype); (b) routine clinical blood tests; (c) biomarkers of inflammation (IL-1, IL-1ra, IL-6, IL-8, IL-10 and TNF $\alpha$ ); (d) altered steroid hormones (cortisol, DHEAS and their ratio).

## 7.2 Methods

### 7.2.1 Participants

Patients over 70 years of age admitted to hospital with DSM-IV-TR diagnosed delirium were recruited. Details of the recruitment are given in more detail in section 2.1.

### 7.2.2 Clinical predictors

Data were collected to provide details of clinical predictors of delirium. These included age, gender, co-morbidity (Charlson co-morbidity index), frailty (Rockwood clinical frailty scale), and acute illness severity (APACHEII). The presence of dementia as recognised on admission was recorded, as was dementia as defined by an IQCODE-SF of  $>3.82$ . This was previously described in chapter 5. Hospital length of stay was recorded at discharge. Routine blood tests collected by the clinical teams were also recorded. These were serum sodium (Na), serum albumin (Alb), the ratio of serum urea over serum creatinine (Ur/Cr) and serum C-reactive protein (CRP).

### 7.2.3 Delirium related predictors

Data were collected to provide details of delirium related predictors. Delirium severity and subtype were recorded at initial assessment as a marker of severity and subtype at admission. Delirium severity was measured using the Delirium Rating Scale Revised Version (DRS-R-98). Delirium subtype was classified by clinical expert assessment using elements of the DSR-R-98 and recognised classifications (Liptzin and Levkoff, 1992, Meagher and Trzepacz, 2000) into hypoactive, hyperactive or mixed subtypes. Duration of delirium was measured by repeated assessment (Monday, Wednesday, and Friday, including review of the medical notes for the days when a clinical assessment was not carried out) of recruited participants during

their in-patient stay and was defined as the total number of delirium days throughout the in-hospital stay.

#### 7.2.4 Biochemical predictors

Blood was taken from recruited participants by venepuncture the morning after admission between 8am and 10am and serum was prepared and stored aliquoted at -80°C for later analysis. Details of methods used for sample preparation and analysis are given in detail in section 2.2. Briefly, serum was prepared and used to measure a panel of inflammatory cytokines (IL-1 $\beta$ , IL-1ra, IL-6, IL-8, IL-10 and TNF $\alpha$ ) using multiplex technology (Biorad, Hertfordshire, UK). Cytokine data were recorded as the proportion of samples that were above the limit of reliable detection (ALD), and the mean and standard error of the true concentration (pg/ml). A ratio of pro-inflammatory to anti-inflammatory cytokines was calculated by adding the sum of the four pro-inflammatory cytokines over the sum of the two anti-inflammatory cytokines  $([IL-1+IL-6+ IL-8 + TNF\alpha]/ [IL-10 + IL-1ra])$ . Serum cortisol and DHEAS were measured using a commercial ELISA assay (IBL International, Hamburg, Germany)

#### 7.2.5 Outcomes

Outcomes were defined at three month follow-up. Mortality and date of death was recorded. An assessment at 3 months in survivors defined whether persistent delirium was present using DSM-IV-TR criteria. New institutionalisation was defined as a participant living in a care home that they were not living in at admission. Adverse outcome was classified as those at 3 months who had died, were in a new care home, or had persistent delirium. Survivors living in their previous place of residence and without persistent delirium were classified as good outcome.

### 7.2.6 Statistical analysis

Descriptive statistics were recorded for the whole group, the good and adverse outcome group, and the survivor and non-survivor group. Depending on normality of data, T-tests or Mann-Whitney U tests were performed to examine differences between continuous variables. Chi-squared test was used to examine difference between categorical data.

Univariate logistic regression analysis was then performed to produce odds ratios (OR) of the chance of adverse outcome at 3 month follow-up. The dependent variable was good or adverse outcome, and the independent variables were variables identified as significantly different between outcome groups. ROC analysis was also performed on continuous significant predictors to try and identify the best cut-off point to create a dichotomous variable.

Multivariable logistic regression was then performed to produce adjusted odds ratios (AOR). The co-variables age, sex, co-morbidity, frailty, function, and illness severity were selected as control variables. It was anticipated that due to the number of events the model may not be stable with a high number of co-variables, so Hosmer–Lemeshow test was used to test the stability of the multivariable model and the number of co-variables chosen to ensure the model is not over fitted. The -2 log likelihood ratios were also used to assess the model fit, and Nagelkerke R square to assess the effect size.

Univariate Cox proportional hazards models were performed to produce hazard ratios of survival. Survivors were used as the reference category. Kaplan-Meier survival curves were generated using significant dichotomous predictors. Difference between curves was analysed using the Wilcoxon Log-rank test. Multivariable Cox proportional hazards were performed, using age, sex, co-morbidity, frailty, function, and illness severity as the co-variables to

produce adjusted hazard ratios. The -2 log likelihood ratio change and the Omnibus Tests of Model Coefficients chi squared test was calculated as a measure of fit for the multivariable model

### 7.3 Results

125 participants with delirium were recruited. Of these, follow-up was completed in 107 (mean age 84.3 years [SD  $\pm$  6.61], 63% female). There was no difference in age, gender, illness severity, CRP, or delirium subtype between those available for follow-up and those unavailable. However, those unavailable for follow-up had less co-morbidity (Charlson index 1 vs 1.5,  $p=0.04$ ), were less frail (Rockwood clinical frailty scale 4 vs 5,  $p=0.02$ ) and had less severe delirium (DRS-R-98 14 vs 19,  $p=0.04$ )

At 3 month follow-up 25/107 (23.4%) had died, 5/107 (4.7%) had persistent delirium and 22/107 (20.6%) were classified as new institutionalisation. Three participants were classified as both persistent delirium and new institutionalisation. A total of 49/107 (45.8%) were classified as adverse outcome. Of the 107 with complete outcome data, 78/107 (73%) had a blood sample taken and analysed for cytokines and adrenal hormones. There was no difference between those with and without blood samples in age, gender, illness severity, co-morbidity, frailty, CRP, delirium severity or delirium subtype. A flowchart of participant flow through the study and outcome classification is presented in Figure 7-1. Median time to follow-up in survivors was 102 days (range 85-181, IQR 57.5)

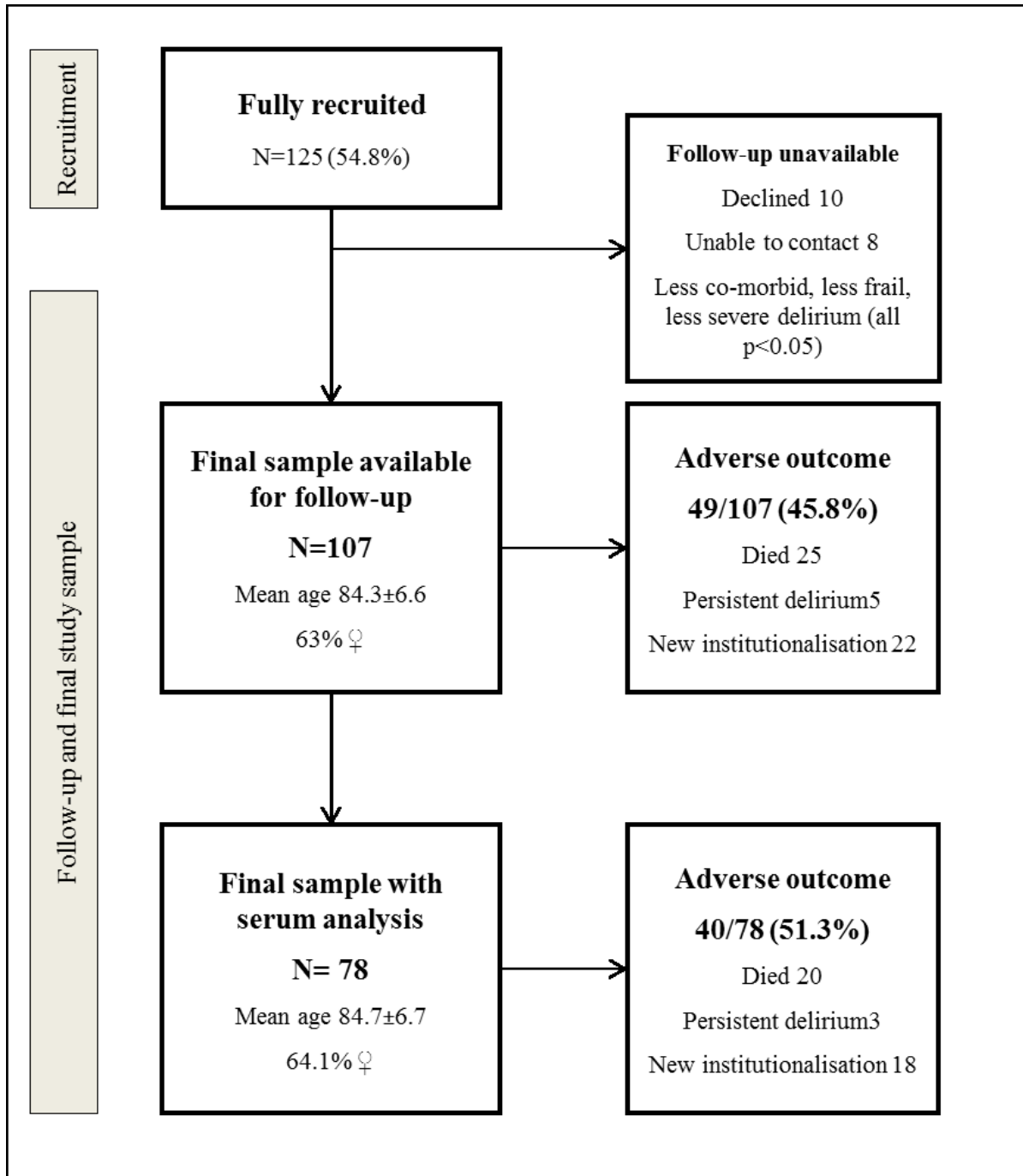


Figure 7-1: Flowchart of participant follow-up and outcome

### 7.3.1 Predicting adverse outcome at 3 months

None of the clinical predictors examined were associated with adverse outcome (see Table 7-1). Of the delirium related predictors, increased delirium severity (DSRS 20 vs 16,  $p=0.03$ ) and longer duration of delirium (6 vs 2 days,  $p<0.0005$ ) were associated with adverse outcome (see Table 7-2). Of the biochemical predictors, only reduced serum TNF $\alpha$  (2.5% ALD vs 18.4% ALD,  $p=0.02$  and 13.6 pg/l vs 27.6 pg/l,  $p=0.03$ ) was associated with adverse outcome. These are illustrated in Table 7-3.

Logistic regression analysis demonstrates that delirium severity by DRS-R-98 (OR 1.08, 95% CI 1.01-1.16) and duration of delirium in days (OR 1.26, 1.11-1.43) predicts adverse outcome at 3 months. Duration of delirium in days also remains a predictor of outcome if those with persistent delirium are excluded (OR 1.25, 1.08-1.43). Duration of delirium to predict adverse outcome had an AUROC of 0.81 (95% CI 0.73-0.90) with a best balanced cut-off of 4/5 days. Using  $>4$  days of delirium as a dichotomous variable predicts a nine fold increased chance of adverse outcome (OR 9.38, 3.75-23.48)

Raised serum TNF $\alpha$  was not predictive of adverse outcome. Using TNF $\alpha$  below the limit of reliable detection (BLD) as a dichotomous variable, this predicts an eight fold increase in the chance of adverse outcome (OR 8.80, 1.03-75.4).

Controlling for age, sex, illness severity, co-morbidity, frailty and function adjusted odds ratios were produced. Delirium severity (AOR 1.08, 1.01-1.16), duration of delirium (AOR 1.28, 1.12-1.46), and delirium  $>4$  days (AOR 11.21, 4.22-29.82) remain significant predictors of adverse outcome. TNF $\alpha$  BLD (AOR 8.79, 1.01-76.8) also remained a significant predictor. The Hosmer–Lemeshow statistic was  $>0.05$  in all models confirming the models are a good



fit. Table 7-4 illustrates this. The -2 log likelihood ratio for all multivariable models decreased, suggesting the multivariable models are not as good a fit as the univariate models.

The DRS-R-98 score where there is a 50% chance of adverse outcome is 19.28. An increase in 5 points on the DRSR-R-98 produces an OR of 1.49 (1.065-2.088). The number of days of delirium where there is a 50% chance of adverse outcome is 5.81 days. An increase in 2 days duration of delirium has an OR of 1.64 (1.23-2.12)

**Table 7-1: Table of clinical predictors showing differences in predictors between good and adverse outcome, and survivors and non-survivors.**

	All n: 107	Good outcome: n: 58	Adverse: outcome: n: 49	p	Survivors: n: 82	Non survivors: n: 25	p
Age, mean years (SD)	84.3 (6.61)	83.4 (6.4)	85.3 (6.1)	0.13	84.4 (6.32)	84.0 (7.01)	0.82
Gender, % female:	62.6	62.0	55.0	0.11	63.9	52.0	0.24
APACHEII	10 (3)	9 (3)	10 (3)	0.53	9 (3)	11 (3)	0.11
Co morbidity	2 (2)	2 (2)	2 (2)	0.32	2(2)	2 (3)	0.23
Frailty	3 (2)	3 (2)	3 (2)	0.87	3(2)	3 (2)	0.30
Function	73 (43)	72.5 (43)	73 (40)	0.74	70 (30)	73 (23)	0.42
Dementia, %	58.9	56.9	61.2	0.69	61.0	52.0	0.49
Length of stay, days:	16 (24)	9.5 (16)	36 (32)	**<0.0003	13 (22)	36 (32)	0.06
Na (mmol/l)	137 (9)	137 (9.6)	137 (6.8)	0.62	137 (8.9)	137 (7.4)	0.77
Alb (g/l)	38 (4.96)	38 (3.07)	38 (4.8)	0.99	38 (4.8)	37 (3.4)	0.10
Urea/Creatinine:	0.098 (0.04)	0.099 (0.04)	0.093 (0.03)	0.84	0.097 (0.03)	0.100 (0.03)	0.19
CRP (mg/l)	63.9 (80.3)	53.9 (57.8)	80.4 (99.4)	0.32	52.8 (68.0)	107.1 (116.3)	*0.04

Co-morbidity is defined by the Charlson Comorbidity Index, frailty by the Rockwood Clinical Frailty scale and function by the Barthel scale. APACHEii defines illness severity. All shown median and IQR in brackets. Dementia is defined by IQCODE >3.82. Na = serum sodium, Alb = serum albumin, Urea/creatinine is the ratio of serum urea over serum creatinine, CRP = C-reactive protein. All shown as mean with standard deviation, \*=statistically significant

**Table 7-2: Table of delirium related predictors showing differences in predictors between good and adverse outcome, and survivors and non-survivors.**

	All n=107	Good outcome n=58	Adverse outcome n=49	p	Survivors n=82	Non- survivors n=25	p
Delirium recognised on admission %	59.8	65.5	53.1	0.33	59.8	60.0	1.00
Delirium severity IDRS-R 98 Median (IQR)	19 (9)	16 (11)	20 (6)	0.03*	18 (9)	19.5 (9)	0.63
Delirium subtype							
Hypoactive %	57	51.7	63.3	0.24	50	80	0.01*
Mixed %	15.9	19.0	12.2		19.5	4.0	
Hyperactive %	27.1	29.3	24.5		30.5	16.0	
Duration of delirium Days (IQR)	3 (6)	2 (2)	6 (8)	<0.0005*	3 (3)	6 (6)	0.001*

\*=statistically significant

**Table 7-3: Table of biochemical predictors showing differences in predictors between good and adverse outcome, and survivors and non-survivors.**

	<b>All n=78</b>	<b>Good outcome n=38</b>	<b>Adverse outcome n=40</b>	<b>p</b>	<b>Alive n=58</b>	<b>Dead n=20</b>	<b>p</b>
<b>IL6 pg/ml</b>	60.3 (19.4)	76.7(39.1)	44.7(7.8)	0.19	63.1(26.3)	52.6 (11.9)	0.09
<b>IL6 ALD %</b>	73.1	65.8	80.0	0.20	67.2	90.0	0.048*
<b>IL8 pg/ml</b>	27.5 (4.9)	28.3 (9.3)	26.8 (3.8)	0.08	25.4 (6.1)	33.7 (6.3)	0.001*
<b>IL8 ALD %</b>	73.1	65.8	80.0	0.20	67.2	90	0.048*
<b>IL10 pg/ml</b>	10.4 (2.5)	11.7 (3.8)	9.5 (3.5)	0.63	12.6 (3.5)	5.57 (2.0)	0.76
<b>IL10 ALD %</b>	16.7	18.4	15.0	0.77	19	10	0.35
<b>TNF<math>\alpha</math> pg/ml</b>	20.9 (6.06)	27.6 (9.2)	13.6 (7.6)	0.03*	28.8 (8.7)	5.4 (1.1)	0.015*
<b>TNF<math>\alpha</math> ALD %</b>	10.3	18.4	2.5	0.027*	13.8	0.0	0.008*
<b>IL1-<math>\alpha</math> pg/ml</b>	71.9 (18.3)	104.9 (36.3)	41.5 (8.0)	0.89	81.2 (24.5)	46.5 (10.2)	0.25
<b>IL1-<math>\alpha</math> ALD %</b>	55.1	55.3	55.0	0.98	51.9	65.0	0.30
<b>IL1-<math>\beta</math> pg/ml</b>	2.1 (0.74)	2.7 (1.1)	1.5 (0.9)	0.21	3.04 (1.1)	0.51 (0.12)	0.045*
<b>IL1-<math>\beta</math> ALD %</b>	6.4	10.5	2.5	0.19	8.6	0.0	0.17
<b>Pro/anti ratio</b>	1.96 (0.42)	1.79 (0.67)	2.13 (0.54)	0.91	1.74 (0.52)	2.36 (0.72)	0.27
<b>Cortisol nmol/l</b>	620.5 (54.7)	599.2 (91.1)	640.0 (63.2)	0.15	575.4 (62.0)	751 (112.6)	0.07
<b>DHEAS <math>\mu</math>mol/l</b>	1.49 (0.12)	1.40 (0.16)	1.60 (0.17)	0.30	1.49 (0.13)	1.52 (0.28)	0.76
<b>Cortisol/DHEA S ratio</b>	1.17 (0.32)	1.59 (0.64)	0.77 (0.15)	0.63	1.19 (0.42)	1.10 (0.27)	0.16

ALD = variable above the level of reliable detection. All data is mean and standard error of the mean

**Table 7-4: Logistic regression models of significant predictor variables.**

Analysis	Model	OR	95% CI	Nagelkerke R <sup>2</sup>	-2 Log likelihood	Hosmer and Lemeshow
Univariate	DRS-R-98	1.08	1.01-1.16	0.08	136.3	
	Delirium duration <sub>cont</sub>	1.26	1.11-1.43	0.28	122.8	
	Delirium <sub>&gt;4 days</sub>	9.38	3.75-23.48	0.30	116.6	
	Serum TNF $\alpha$ (pg/ml)	0.99	0.97-1.01	0.06	48.3	
	TNF $\alpha$ BLD	8.80	1.03-75.4	0.10	102.1	
Multivariable	DRS-R-98	1.08	1.01-1.15	0.10	134.6	0.23
	Delirium duration <sub>cont</sub>	1.28	1.12-1.46	0.31	118.9	0.09
	Delirium <sub>&gt;4 days</sub>	11.21	4.22-29.82	0.35	115.6	0.79
	TNF $\alpha$ below LD + control	8.79	1.01-76.8	0.12	100.8	0.86

DRS-R-98 = Delirium rating scale. Multivariable analysis controlling for age, sex, illness severity (APACHEII), co-morbidity (Charlson Index), frailty (Rockwood Clinical Frailty Scale) and function (Barthel)

### 7.3.2 Predicting survival at 3 months

Figure 7-2 illustrates a survival curve for the complete cohort with median time to death (36 days) and follow-up (102 days). Of the clinical predictors tested, only raised serum CRP was associated with mortality at 3 months (107.1 mg/l vs 52.81mg/l,  $p=0.038$ , see Table 7-1). Duration of delirium (6 days vs 3 days,  $p=0.001$ ) and hypoactive subtype (90% vs 67.2%,  $p=0.048$ ) were associated with mortality at 3 months (see Table 7-2). Raised IL-6 (90% ALD vs 63% ALD), raised IL-8 (90% vs 67.2%,  $p=0.048$  and 33.7 pg/ml vs 25.4 pg/ml,  $p=0.001$ ), reduced TNF $\alpha$  (0% ALD vs 13.8% ALD,  $p=0.008$  and 5.4 pg/ml vs 28.8 pg/ml,  $p=0.015$ ), and reduced IL-1 $\beta$  (0.51 pg/ml vs 3.04 pg/ml,  $p=0.045$ ) were associated with mortality at 3 months. This is illustrated in Table 7-3.

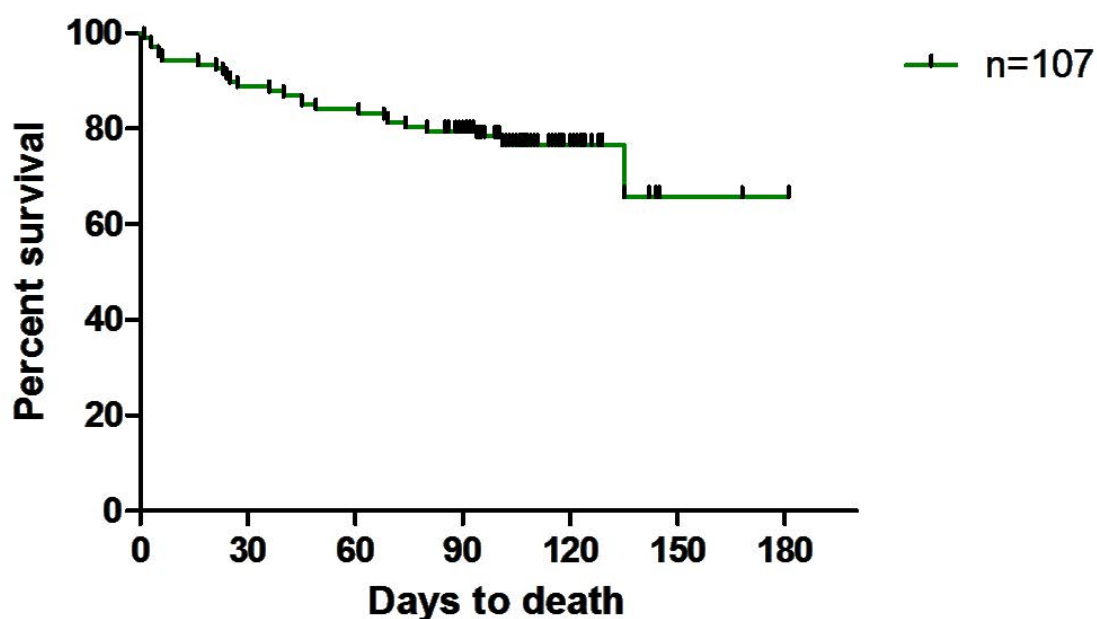
Cox proportional hazards models to predict risk of death over 3 months was used. CRP predicted mortality (HR 1.007, 95% CI 1.003-1.011) with an AUROC of 0.63 and best cut-off of 69/70 mg/l. Therefore a dichotomous variable of CRP >69mg/L was created which predicts a 3 fold increase in mortality (HR 3.21, 1.45-7.10). Delirium duration in days (HR 1.05, 1.02-1.09), delirium duration >4 days (HR 3.20, 1.44-7.13) and the hypoactive subtype (HR 3.56, 1.33-9.56) predicted mortality. The significant altered biological predictors all did not predict mortality at 3 months. Figure 7-3 demonstrates Kaplan Meier survival curves for the three identified dichotomous variables

Multivariable cox proportional hazards models were performed. Controlling for age, illness severity, and co-morbidity produced a stable model. Raised serum CRP (HR 1.006, 1.002-1.011) and serum CRP >69mg/l (HR 2.81, 1.24-6.40) remained significant after control. Delirium duration in days (HR 1.08, 1.03-1.12), delirium > 4 days (HR 3.18, 1.42-7.16), and the hypoactive subtype (HR 3.13, 1.15-8.52) remained significant after adjustment. The -2

log likelihood ratios for all the multivariable models fell, suggesting the multivariable models are not as good a fit as the univariate model.

### 7.3.3 Infection and adverse outcomes

The presence of infection, though not confirmed microbiologically, was defined as a cut-off of serum CRP >40mg/l, where values higher than 40mg/l are considered to be infective. IL-6, IL8, and IL-1ra were significantly higher in the infected group, and the TNF $\alpha$  ALD significantly lower (34 of 78). There was also a trend towards lower serum TNF $\alpha$  and IL-1 $\beta$  in the infected group. Table 7-6 illustrates this. Examining the infection group only (34/78), IL-8 was higher in the non-survivor group compared to the survivors group ( $p=0.046$ ), and there was a trend towards lower TNF and IL-1ra in both the adverse outcomes group and the non-survivors. Table 7-7 illustrates this.



#### Survival

Survivors (n=82)		Non-survivors (n=25)	
Time to follow-up - days		Time to death -days	
Median	102	Median	36
Range	85-181	Range	1-135
IQR	21.25	IQR	57.5

Figure 7-2: Survival curve of entire cohort. Dash on the lines illustrate censored points



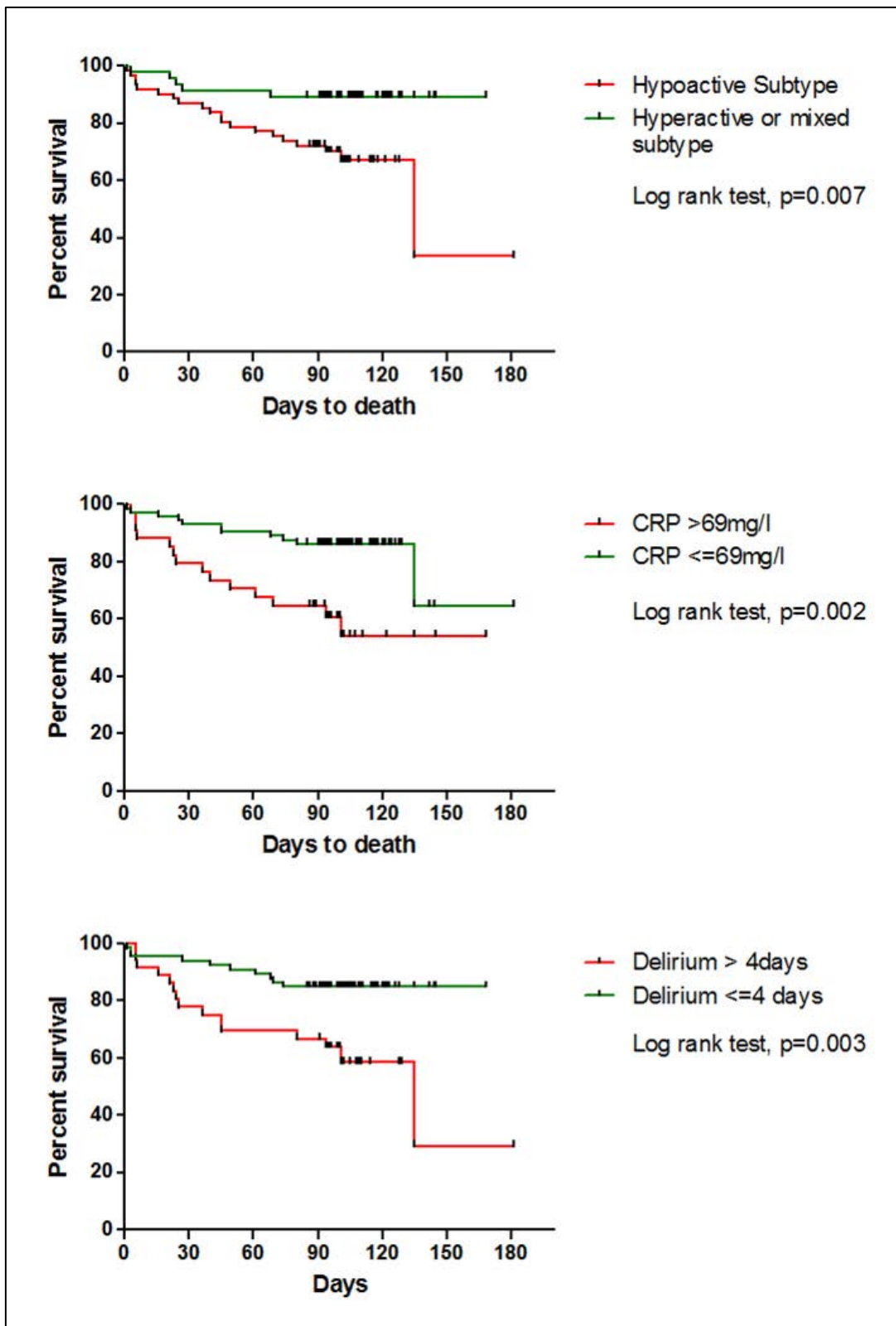


Figure 7-3: Kaplan-Meier survival curves for dichotomous variables associated with mortality

**Table 7-5: Cox proportional hazards models**

Analysis	Model	HR	95% CI	-2 Log Likelihood	Test of model co-efficient
Univariate	Delirium duration <sub>cont</sub>	1.05	1.02-1.09	212.8	0.002
	Delirium <sub>&gt;4 days</sub>	3.19	1.44-7.13	210.4	0.003
	Hypoactive delirium	3.56	1.33-9.53	213.1	0.007
	CRP	1.007	1.003-1.011	209.8	0.001
	IL-6 ALD	2.76	0.632-12.10	141.3	0.710
	IL-8	1.00	0.99-1.01	140.8	0.760
	IL-8 ALD	2.98	0.69-12.97	140.8	0.110
	TNF- $\alpha$	0.91	0.78-1.06	62.7	0.160
	TNF- $\alpha$ BLD	0.04	0.00-34.23	140.2	0.150
	IL-1 $\beta$	0.48	0.21-1.09	52.0	0.070
Multivariable	Delirium duration <sub>cont</sub>	1.08	1.03-1.12	205.0	0.002
	Delirium <sub>&gt;4 days</sub>	3.18	1.42-7.16	206.0	0.008
	Hypoactive subtype	3.13	1.15-8.52	210.7	0.04
	CRP	1.006	1.002-1.011	207.6	0.005
	CRP >69mg/l	2.81	1.24-6.40	210.6	0.019

Multivariable analysis controlling for age, sex, illness severity (APACHEII), co-morbidity (Charlson Index), frailty (Rockwood Clinical Frailty Scale) and function (Barthel). ALD = above the limit of reliable detection, BLD = below the level of reliable detection

**Table 7-6: Table 1 6: Comparison of inflammatory cytokines by infection status. Infection = CRP>40mg/l.**

	No infection	Infection	
	n=43	n=34	p
IL6 pg/ml	55.1 (31.7)	59.9 (11.4)	0.002*
IL6 ALD %	63.6	85.3	0.033*
IL8 pg/ml	27.1 (8.1)	28.1 (4.1)	0.024*
IL8 ALD %	68.2	79.4	0.246
IL10 pg/ml	8.9 (3.1)	6.6 (2.3)	0.486
IL10 ALD %	15.9	17.6	0.838
TNF $\alpha$ pg/ml	12.6 (5.0)	5.9 (2.5)	0.385
TNF $\alpha$ ALD %	13.6	5.9	0.263
IL1-ra pg/ml	60.5 (19.8)	80.4 (31.5)	0.011*
IL1-ra ALD %	43.5	70.6	0.016*
IL1- $\beta$ pg/ml	1.01 (0.5)	0.36 (0.1)	0.910
IL1- $\beta$ ALD %	11.4	0.0	0.042*

**Table 7-7: Table of biochemical predictors showing differences in predictors between good and adverse outcome, and survivors and non-survivors, in the infection group (n=34)**

	Infection n=34	Good outcome n=13	Adverse outcome n=21	p	Alive n=21	Dead n=13	p
IL6 pg/ml	59.9 (11.4)	76.7(24.8)	49.5 (10.5)	0.71	67.0 (16.9)	48.4 (12.7)	0.92
IL6 ALD %	85.3	76.9	90.5	0.28	81.0	92.3	0.36
IL8 pg/ml	28.1 (4.1)	19.7 (3.5)	33.2 (6.1)	0.18	20.1 (2.6)	40.0 (8.9)	0.04*
IL8 ALD %	79.4	76.9	81.0	0.78	71.4	92.3	0.14
IL10 pg/ml	6.6 (2.3)	4.9 (1.6)	7.6 (3.5)	0.83	6.9 (3.3)	6.0 (2.7)	0.60
IL10 ALD %	17.6	23.1	14.3	0.52	19.0	15.4	0.78
TNF $\alpha$ pg/ml	5.9 (2.5)	10.7 (6.1)	2.9 (0.9)	0.23	7.6 (3.9)	3.1 (0.8)	0.92
TNF $\alpha$ ALD %	5.9	15.4	0.0	0.06	9.5	0.0	0.25
IL1-ra pg/ml	80.4 (31.5)	132.3 (80)	48.2 (12.0)	0.34	99.2 (50.3)	49.9 (13.7)	0.97
IL1-ra ALD %	70.6	76.9	66.7	0.52	66.7	76.9	0.52
IL1- $\beta$ pg/ml	0.36 (0.1)	0.47 (1.1)	0.02 (0.9)	0.38	0.39 (0.12)	0.30 (0.12)	0.89
IL1- $\beta$ ALD %	0.0	0.0	0.0	NA	0.0	0.0	NA

## 7.4 Discussion

Older people with delirium had adverse outcomes at three months follow-up. Nearly half had either died, were in a new care home, or still had delirium. Nearly one in four (23.4%) had died. The relationships between a number of key clinical, delirium related and biochemical predictors of adverse outcomes in delirium have been identified.

### *Delirium related predictors*

Delirium duration appears to be the most important predictor of outcome. Taking age, illness severity and co-morbidity into account every day of delirium presents a 28% increased chance of adverse outcome and an 8% increased risk of death. An increase in delirium duration of two days raised the chance of adverse outcome by 64%. Delirium lasting greater than 4 days, as opposed to less than 4 days or no delirium, increased the chance of adverse outcome by 11 fold, and the risk of death by three fold. This is in keeping with two studies that have specifically examined length of delirium in days as a predictor of adverse outcomes. A study of older medical inpatients reported a 12% increased risk of death (HR 1.12,  $p < 0.05$ ) for every increase in delirium duration of 48 hours. This was over a three month follow-up and is in the same setting as the current study (Gonzalez et al., 2009). In hip fracture patients an increase in delirium duration of one day was associated with a 17% increased risk of death (HR of 1.17, 95% CI 1.07-1.28) over six months follow-up (Bellelli et al., 2014a).

The hypoactive motor subtype at admission, as opposed to the hyperactive or mixed subtype, increased the risk of death by over 3 times. The literature is conflicting on which subtype is more likely to predict adverse outcome and this relationship has been investigated in six previous studies. Three studies have shown an association between the hypoactive subtype

and adverse outcomes (Kiely et al., 2007, Meagher et al., 2011, Yang et al., 2009), a single study has shown the hyperactive subtype predicts adverse outcome (Marcantonio et al., 2002) and two studies have shown no association (Slor et al., 2013, DeCrane et al., 2011). However, four studies were in post-acute or palliative care settings and two in hip fracture patients. No studies have investigated delirium subtype and outcomes in medical patients. It is also worth noting the different ways delirium subtype was classified. Single domains within a delirium severity scale (the MDAS) were used in three studies, and the other two used single domains from the DRS-R-98 and the clinical assessment of confusion scale A (CAC-A). Only one study, set in palliative care patients, used a recognised subtyping scale, the Delirium Motor Subtype scale (DMSS). Details of these studies are in section 6.4. The current findings used a clinical assessment based on recognised descriptions of the different motor subtypes (section 2.1.7.2) as it was felt this would give as close to a reference diagnosis as possible. Future research should perhaps therefore look at the standardisation of delirium subtype classification to allow comparison between studies.

Delirium severity is also important, increasing the chance of adverse outcome by 8% for every increase in DRS-R-98 score (scale 0-39, median score 19). An increase in five points increased the chance of adverse outcome by 50%. There was no relationship between delirium severity and mortality however. This result is in keeping with three previous studies in the literature, however all three studies used the Memorial Delirium Assessment Scale (MDAS, scale 0-30). Two studies investigated delirium severity in medical inpatients. One found an association with delirium severity and poor recovery (defined as death or new institutionalisation), with delirium defined as 'severe' having a 16% increased risk (Dasgupta and Brymer, 2014). Delirium severity, as defined by an MDAS score of >24 was associated with mortality at three months (Kelly et al., 2001). The third study was in hip fracture patients

and reported an association between delirium severity (MDAS >12.44) and a three-fold increased risk of six month mortality or new institutionalisation. It is interesting that two of these studies have found an association only with a combined outcome of death and new-institutionalisation, rather than mortality alone, as in the present study.

*Biochemical and inflammatory changes as predictors*

Biochemical changes related to inflammation have also been identified here as being associated with adverse outcomes and mortality. The pro-inflammatory cytokines IL-6 and IL-8 were higher in the non-survivors, whereas the pro-inflammatory cytokines TNF $\alpha$  and IL-1 $\beta$  were lower in the non-survivors. Raised CRP, which is pro-inflammatory, was associated with risk of death and a CRP of >69mg/l on admission with delirium increases the risk of death nearly threefold. However, TNF $\alpha$  below the limit of reliable detection was associated with an eight fold increased chance of adverse outcome. Although not significant there was a trend toward higher cortisol being associated with mortality. There was no association between the anti-inflammatory cytokines IL-1ra and IL-10 and adverse outcomes or mortality. These contradictory results suggest that a linear relationship based on increased inflammation leading to worse outcomes is not valid. They demonstrate that the immune-inflammatory response in delirium is disordered, rather than simply pro-inflammatory. This may in some way explain why studies of inflammation in delirium have so far proved contradictory.

There are a number of possibilities to explain the results for pro-inflammatory cytokines. Peripheral monocytes produce the four pro-inflammatory cytokines in response to acute stress equally, so it is unlikely the imbalance is due to a change in monocyte population or function. It is possible that the raised IL6 and IL8 are centrally derived (from activated microglial cells) and cross a permeable blood brain barrier. Since delirium duration is also associated with

adverse outcome, it could be hypothesised that those with adverse outcome have a higher degree and longer duration of central inflammatory insult resulting in the driving of neurodegeneration. Another possibility may be due to altered cytokine kinetics. The early release of peripheral IL6 and slower release of TNF $\alpha$  and IL-1 $\beta$  have been observed in ischaemic stroke patients (Fassbender et al., 1994). The time course of the cytokines IL-6 and IL-8 have been studied in hip fracture patients (van Munster et al., 2008) and show a peak immediately after the fracture, with resolution by 48 hours after the fracture. Blood in the current study was sampled at a single time point, within 24 hours of admission. Soluble TNF $\alpha$  receptors STNF1 and STNF2 are associated with delirium in critically ill patients (Ritter et al., 2014) and if these are raised in the current cohort, this may account for the low levels of measurable TNF $\alpha$ . Follow on studies with the remaining stored samples could test this hypothesis.

It may be that infection is the main driver of outcomes in delirium, which would be supported by high levels of IL-8 (a neutrophil attractant also produced by neutrophils themselves once primed) and CRP found associated with poor outcomes here. However, it is not possible to reliably include or exclude infection, especially in older patients. Older patients will typically present with multifactorial precipitants of delirium. Traditional tools such as SIRS criteria, or positive microbiology, are likely to have false positive and false negative classifications respectively. Three recent papers, all in critical care delirium, have attempted to look at whether septic delirium is biochemically different from non-septic delirium. Raised IL-8 was associated with delirium in those classified as infected, as opposed to raised IL-10 which was associated with delirium in a non-infected group (van den Boogaard et al., 2011). Raised IL-10 was not found to be associated with poor outcome here. CRP and pro-calcitonin were found to be associated with delirium irrespective of a diagnosis of sepsis (McGrane et al.,



2011), and similarly IL-1b, STNFR1 and STNFR2 and adiponectin are associated with delirium independent of sepsis (Ritter et al., 2014).

In attempting to classify patients in the current study by infection (cut-off of serum CRP >40mg/l) serum IL-6 and IL-8 were higher in those with infection, suggesting that infection may be a driver in the raised IL-6 and IL-8.

Caution should be advised given that these are peripheral cytokines which may not give a good indication of inflammatory changes in the central nervous system. However they do inform the nature of the peripheral inflammatory response. In future research, central cytokines should also be paired with peripheral cytokines to elucidate the relationship between peripheral and central inflammatory response and outcomes. However, central cytokines are difficult to measure in a non-surgical population without access to routine CSF sampling. Elevated S100 $\beta$ , a marker of neuronal damage, has been used as peripheral proxy of central inflammation and is raised in the serum of similar medical patients with delirium (van Munster et al., 2010). Other studies have looked at paired central CSF values and peripheral serum values of cytokines to illustrate a specific central inflammatory response (and possible evidence for microglial activation, see 1.1.7.3). A study of hip fracture patients found elevated IL-1 $\beta$  in CSF, but no correlation with serum IL-1 $\beta$ . This suggests the IL-1 $\beta$  is centrally produced (Cape et al., 2014) (see 1.1.7.4)

When comparing the cytokine values of older people with delirium in the current study with other relevant cohorts, the delirium values were higher than in those without delirium from a community dwelling sample (Baylis et al., 2013) and those without delirium and hip fracture (personal communication, Dr N Duggal), but lower than in older patients with an acute burn injury (personal communication, Dr P Hampson). See Table 7-8.

*HPA axis changes*

There was no difference between cortisol, DHEAS or their ratio between outcome groups. This is in contrast to findings in a prospective cohort study on older stroke patients. Here, higher cortisol on admission was associated with mortality within seven days of stroke (OR for rise in cortisol of 100 nmol/l 1.9, 1.01-3.8), but not at three months (Christensen et al., 2004). DHEAS was not measured in this cohort.

However, in the current study the true values of cortisol were higher than reported in community dwelling populations and in those following hip fracture. Also, the cortisol/DHEAS ratio was higher. See Table 7-8 for comparisons. Since it appears that delirium as a condition demonstrates higher cortisol and a raised cortisol/DHEAS ratio, it may be that any changes in an already stressed system are not detectable. Any further study into these relationships should attempt to control for sepsis and examine the whole steroid hormone pathway. This is warranted, especially given the down-regulation of DHEA sulfotransferase seen in patients with sepsis (Arlt et al., 2006). This enzyme converts DHEA to DHEAS, thus reducing levels of DHEAS which is known to enhance neutrophil bactericidal function (Radford et al., 2010), suggesting that the relationship between sepsis and HPA axis dysregulation may be important with delirium.

*Negative relationships*

Age, frailty, function or dementia did not predict adverse outcome or death in this study despite these having been previously reported as predictors of adverse outcomes. The negative result for dementia may be due to the increasing prevalence of dementia now being seen in hospital, leading to a higher incidence of dementia in the study group. A similar study examining dementia as a predictor of outcome in delirium found dementia to be protective

(McCusker et al., 2002). This was a cohort of acute medical admissions with a similar prevalence of dementia among those with delirium (68% compared to 59% in this cohort), but the prevalence of dementia in all those admitted is unknown. Two other studies report dementia as a predictor of adverse outcome (Yang et al., 2009, Morandi et al., 2014) but these are both set in post-acute care and they report a prevalence of dementia among delirium of 68% and 37% respectively.

Despite depression being a previously recognised predictor this was not measured as it was felt added assessment of depression would be too burdensome. Also, depression is under-recognised in older people by primary care, with up to 50% of cases undiagnosed (Simon et al., 1999). Because of this it was felt a documented diagnosis would not be sufficiently robust. Previous studies of depression as a predictor used the Geriatric Depression Scale (GDS-15). Both these cohorts were not delirious at recruitment and the GDS was administered early in the admission (Givens et al., 2009, Givens et al., 2008). Given the nature of the study cohort in this thesis this method would not have been possible, as the GDS would be difficult to conduct in patients with delirium and has not been validated in this way.

These results are likely to be representative as they were taken from a generalizable cohort with robust follow-up. The measured values for cytokines and cortisol were similar to that seen in other cohorts of older patients with delirium (Table 7-8). There was an attrition of 18 of 125 who were not followed up. This group were fitter, being less frail and having less comorbidity. They also experienced less severe delirium. This may have biased results as the degree of adverse outcome may have been higher in the followed-up group, compared to the fitter group not followed up. Measures of delirium subtype are often difficult in practice. The current study used a clinical assessment to define delirium subtype against a recognised

schema (Liptzin and Levkoff, 1992) rather than a delirium subtype score such as the Delirium Motor Subtype scale (DMSS) and the Delirium Motor Checklist (DMC). This was due to the practicalities of adding further assessments in a potentially vulnerable cohort and that there is poor concordance of subtype classification between different methods used (Meagher et al., 2008). Since the study was designed, a brief motor subtype scale, the DMSS-4 (Meagher et al., 2014a) has been developed and future research could use this to allow for more standardised classification of subtype. It should also be noted that the increased risk of death was associated with hypoactive delirium on admission, as motor subtype was not followed during stay. However the motor subtype of delirium is relatively consistent over the course of delirium when studied in a cohort of palliative care patients (Meagher et al., 2011). No studies have specifically examined the persistence of motor subtype in older medical patients.

In clinical practice, delirium motor subtype and CRP can be easily measured on admission to guide management. Motor subtype cannot be altered, but assessment of subtype should become routine to inform prognosis, and the DMSS-4 would be a practical tool. Manipulation of the inflammatory response with known interventions such as early antibiotic therapy or rigorous infection management could potentially reduce adverse outcomes. Delirium duration is also a potential target for interventions to improve outcomes. What is not known is if interventions to reduce duration of delirium would also improve outcomes, but this is plausible. Delirium prevention strategies have been shown to reduce delirium incidence, and also the duration of delirium (Inouye et al., 1999). Pharmacological management of delirium with haloperidol, although not clearly shown to be of benefit in delirium does have an effect on delirium duration. A trial of haloperidol prophylaxis in elective hip surgery, while showing no reduction in delirium incidence, did demonstrate a reduction in delirium severity and duration in the treatment arm (Kalisvaart et al., 2005). A

randomised trial of haloperidol to treat delirium in hospitalised patients with AIDS showed reduction in both delirium severity and duration in the treatment arm (Breitbart et al., 1996).

In conclusion, delirium duration, severity, and the hypoactive subtype, as well as a dysregulated inflammatory response, are associated with adverse outcomes in hospitalised older adults.

**Table 7-8 Comparison of immune-endocrine findings in the current study with other relevant cohorts.**

	Cortisol nmol/l	DHEAS μmol/l	Cortisol: DHEAS ratio	IL-6	IL-8	IL-10	TNFα	IL-1ra	IL-1β
Current study Delirium, 84yrs, n=78	620.5	1.49	1.17	60.3	27.5	10.4	20.9	71.9	2.1
Philips et al 2013 Acute hip#, 84yrs, n=101			2.2 dep 0.8 nondep						
Baylis et al 2012 Community, 65-70yrs, n=254	308 ♂ 274 ♀	2.18 ♂ 1.49 ♀	0.12 ♂ 0.19 ♀	1.2 ♂ 0.9 ♀		2.3 ♂ 1.9 ♀			11.3 ♂ 18.3 ♀
Christensen et al 2004 Acute stroke, 74 yrs, n=185	676								
Trivedi et al 2001 Community dwelling, 65-76 yrs, n=2134		2.98							
SIFTI study Acute burn injury, >65 yrs, n=10				337.9	171.0	79.2	5.5	345.2	0.77
Van Munster et al 2012 Delirium and hip#, age 85 yrs, n=62	646			84.3	21.5				

All cytokine values in pg/ml, ♂ = male, ♀=female

## 8 General discussion

This thesis has examined the relationships between delirium and dementia in the general hospital and evaluated pragmatic methods of screening and follow-up of older patients with delirium. Chapter 1 discussed clinical and pathophysiological aspects of delirium, the clinical presentation of dementia in general hospitals, and the interdependent relationship between the two conditions. Chapter 3 described the prevalence of dementia and MCI in older people presenting with delirium, and described the proportions of these conditions that were not previously diagnosed. Chapter 4 reported on current tools available to identify dementia in general hospitals, and chapter 5 described the pragmatic solution of informant tools to identify dementia and cognitive impairment in those presenting to hospital with delirium. Chapter 6 then reported on identified predictors of adverse outcome in patients with delirium and how they may stratify follow-up. Finally, chapter 7 expanded on those results and identified both clinical and biochemical predictors of both adverse outcome and mortality in older people with delirium.

This final chapter will first summarise the key results of these chapters referring to the original three core questions of the thesis. It will then discuss general strengths and limitations. The case study presented in chapter 1 will then be used to illustrate the contributions to knowledge the thesis has made. Finally, future research directions will be discussed



## 8.1 Main findings

The first research question addressed in the thesis was; what is the prevalence of combined cognitive impairment (dementia and mild cognitive impairment) in older people with delirium? A prospective cohort of older people presenting to hospital with delirium was formed to answer this question. Of those presenting with delirium four in five had cognitive impairment. 17% had MCI, 57% had dementia, 6% had a persistent delirium and 20% had no cognitive impairment. One in five (21%) had dementia that had not previously been diagnosed and no-one with MCI had this previously diagnosed. Therefore two in five (38%) of older people presenting to hospital with delirium had an undiagnosed combined cognitive impairment (MCI or dementia)

The second research question addressed was; what is the validity and accuracy of informant tools to detect dementia in older people with delirium? A systematic review found few validated screening instruments to detect dementia in general hospitals, with only nine studies reporting six discrete instruments. The AMTS, at a cut off of  $<7$ , was the best studied instrument. It had good discriminatory ability, a pooled sensitivity of 81%, a specificity of 85%, and an AUC of 0.88. No studies of the AMTS included patients with delirium. A single informant instrument, the IQCODE had been validated in medical inpatients, but not in patients with delirium. In the current cohort study informant tools, the IQCODE and the AD8, had excellent discriminatory ability to detect dementia. The IQCODE, at a cut-off of  $>3.82$ , had a sensitivity of 91%, a specificity of 93% and an AUC of 0.93. The AD8, at a cut-off of  $>6$ , had a sensitivity of 83%, a specificity of 90% and an AUC of 0.91. The IQCODE and AD8 were also able to identify those with combined cognitive impairment (MCI or dementia) with good discriminatory ability.

The final research question addressed in the thesis was; among older people with delirium in the general hospital, which clinical and biochemical features are associated with adverse outcomes? Important predictors of adverse outcomes identified in a systematic review were delirium duration, delirium subtype, delirium severity and co-morbid depression and dementia. The cohort study identified delirium duration as a predictor of adverse outcome (death, new institutionalisation or persistent delirium) and mortality. Every day of delirium increased the chance of adverse outcome at three months by 28 % (AOR 1.28). The hypoactive subtype was associated with a three-fold increased risk of death by three months (HR 3.13) and increasing delirium severity by DRS-R-98 was associated with an increased chance of adverse outcomes at three months (AOR 1.08). Biochemical predictors demonstrated a more complex relationship between inflammation and delirium outcome. A CRP >69mg/l was associated with nearly a three-fold increased risk of death (HR 2.81) and raised IL-6 and IL-8 but lower TNF and IL-1 were associated with adverse outcomes. An undetectable TNF was associated with an 8 fold chance of adverse outcome at three months (AOR 8.79)

## 8.2 Strengths and limitations

### 8.2.1 Derivation of the study sample

A major strength is that the prospective cohort study produced a representative sample of older patients presenting to hospital with prevalent delirium. Participants were screened using a two stage process, with both formal cognitive testing and history being used initially to then formally diagnose delirium. Delirium was diagnosed by standardised criteria from the DSM-IV-TR. This ensured that there would have been low false positive and false negative diagnoses of delirium. The prevalence of delirium in the study, of 17% (95% confidence

interval 15-19%), is similar to that found in similar studies in the same setting (Collins et al., 2010). This suggests that screening process was robust. To ensure the cohort was as representative of the real world as possible, participants were selected from a general, unselected medical admissions unit and the exclusion criteria were kept to a minimum. The age, degree of co-morbidity and frailty of the sample was very representative of real world practice. However there were limitations to this process as well. Screening did not take place on consecutive days, but in 142 days over an 18 month period. Also, a group of potential participants (341 of 1668, 20%) were not screened due to logistical reasons (they were not available on the ward at the time, they were too ill to even approach for screening). Unfortunately it is not possible to evaluate the risk of selection bias as no clinical information is available for the group not screened.

Only half of those diagnosed with delirium were subsequently recruited (125 of 228, 55%). There was no difference in age or gender between those recruited and those not however, so the risk of selection bias is estimated to be low. Potential participants with delirium were not recruited for three reasons. Firstly, the main reason for not recruiting was the lack of available consultee. The recruitment to the study was time dependant, as blood samples needed to be taken by the next morning, so this meant that potential consultees and informants needed to be at the hospital on the day of screening. This led to a greater than anticipated number of people who were not recruited. However, a key strength was that of those approached, only 2 of 127 declined to participate. Secondly, potential participants were not recruited if they were felt at risk of imminent death (22 of 228). By excluding these participants the mortality rate of delirium was likely to have been under estimated. This may have led to reporting bias in the interpretation of the outcome data. Also, it would be expected that the prevalence of dementia would have been higher in those who died, thus

potentially underestimating the true proportion of participants with dementia and MCI. Thirdly, potential participants who were not competent in the English language were excluded as it was felt they would not be able to complete cognitive assessment at follow-up (15 of 228). Given that a potential advantage of informant tools is to diagnose cognitive impairment and dementia in those with language difficulties this was a shame. Future research should aim to include persons with language and communication problems as they may be group who may benefit most from interventions using informant tools. However, the acceptance and recognition of cognitive impairment differs between different cultural backgrounds, especially southeast Asian groups, who were the majority of people excluded (Giebel et al., 2015).

### 8.2.2 Research measures

The screening, recruitment and assessments were all carried out by the author. This process was a strength, as the author is a specialist in geriatric medicine and expert in the cognitive assessment of older people in hospital. The author is also experienced in talking to patients and relatives in high stress situations, and this may have contributed to the high recruitment to the study once a consultee was available. However, the use of a single assessor is a potential limitation. The screening was labour intensive, so may not be easily translatable into real world clinical practice. However, brief tools with good discrimination to detect delirium are now available and would be recommended (Bellelli et al., 2014b). However, the informant tools used were chosen as they are freely available and easy to use, so this part of the assessment is hoped to be easily translatable into routine clinical practice. Risk of interviewer bias from the single assessor at three month follow-up was minimised by the informant completing the informant tools in private, meaning the three month follow-up assessments were carried out blinded to the results of the IQCODE and AD8.

It was not possible to obtain blood samples in 34 of 125 (27%) study participants. It was anticipated that the group with no blood sample may be more likely to have the hyperactive motor subtype and be more acutely unwell. However, there was no difference in age, disease severity, or delirium motor subtype between the groups with and without blood samples. This suggests the risk of selection bias at this stage is low. Blood samples were all collected at a routine time of day to try and avoid differences with circadian rhythm. A limitation of the analysis of the biochemical predictors and inflammatory profiles was that a single time point did not allow for examination of the resolution of the inflammatory response. A repeat blood sample and cytokine analysis during the hospital admission and at three month follow-up would have allowed this, however it was felt this would add to the burden on participants and may have led to more participants declining follow-up.

### 8.2.3 Statistical power

The project was statistically powered to validate the IQCODE and AB8 to diagnose dementia (see chapter 2.3). The study recruited to the planned target, so the results of the diagnostic test accuracy of the informant tools have adequate power. However, the study is likely underpowered to assess the relationship between covariates and outcomes. Biochemical predictor covariates were only available in 91 of 125, meaning only 78 of 103 with full follow-up data.

### 8.2.4 Attrition at three month follow-up

There was inevitable attrition of participants between hospital discharge and three month follow-up (18 of 125, 14%). It is difficult to assess if this attrition rate at follow-up is similar to previous studies as most outcome studies of delirium to date have relied on national death registers to record mortality. Of the 27 studies identified in chapter six, 19 recorded follow-

up by national death records, telephone interview, or used only in-hospital outcomes only. Six studies used follow-up interviews at three or six months but did not report follow-up attrition rates. One study reported the only 13 of 62 hip fracture patients with delirium were followed up at three months (Slor et al., 2013). The reasons for this large attrition rate are not reported.

In the current study eight participants were uncontactable when arranging three month follow-up. It is not clear therefore whether they had averse or good outcome so it is not possible to assess for risk of attrition bias in terms of investigating outcomes. 10 participants declined follow-up at three months. Knowing this participant group were survivors suggests they may have been more likely to have had a good outcome, but it was not possible to ascertain new institutionalisation, or persistent delirium. The group that were not followed-up had less comorbidity, less severe acute illness, and less severe delirium (xref to prediction chapter). Therefore there is a risk of attrition bias at this point, as it would be expected that this group may be more likely to have had better outcomes.

20% of the cohort died after recruitment and before three month follow-up (25 of 125). This mortality rate is similar to reported rates of 14.5 to 37.0% of in-hospital mortality in medical inpatients (Siddiqi et al., 2006). There was no difference in demographics between survivors and non-survivors, non survivors were more likely to have hypoactive delirium (xref prediction chap). This group of non-survivors were included in the analysis of outcome, but were not included in the analysis of underlying combined cognitive disorders, or the validation of the IQCODE and AD8. It would be anticipated that the non-survivors had a greater prevalence of dementia, given the adverse outcomes associated with dementia, thus causing an underestimation of the true prevalence of dementia and MCI in the cohort.

However, retrospectively applying the IQCODE cut-off of  $>3.82$ , showed no difference between the survivors and non survivors (58% vs 48% respectively,  $p=0.48$ ). Therefore the risk of attrition bias is low.

Applying the Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies to the study reveals a low risk of bias across the three domains of selection, comparability and outcome (Wells et al., 2012). Applying the QUADAS-2, which is designed to assess the quality of primary diagnostic accuracy studies, reveals a low risk of bias and low concern about applicability across its four domains (Whiting et al., 2011).

### 8.3 Context and wider impact

The wider context and impact of these findings can be illustrated by revisiting the case study introduced in section 1.1.1. Mrs TJ is an older woman who was admitted to hospital with hypoactive delirium. The application of these advances in knowledge provides a pragmatic framework to improve her management and follow-up. Although there is no previous diagnosis of dementia, it is now known she is at high risk of having cognitive impairment, either MCI or dementia. The relatives have raised concern about her cognition over the past year, so an IQCODE is completed by her daughter. The IQCODE score is 4.06/5.00 suggesting she has dementia. Her delirium severity is measured using DRS-R-98 and is 23/39. This high delirium severity, the hypoactive subtype, and raised serum CRP identifies her as being at high risk of adverse outcome, including persistent delirium, new institutionalisation, and mortality. The identification of this ensures she is considered high-risk by the medical staff. Appropriate discussions about prognosis can now be had with the patients and her relatives. Mrs TJ recovers from her delirium, and the now identified

dementia ensures she is managed on a ward specialising in dementia care during her ongoing recovery. This potentially reduces her risk of hospital complications and allows for appropriate discharge planning to take place. On discharge she is referred to specialist memory services for consideration of treatment for her dementia, and her general practitioner is formed about her ongoing risk of adverse outcome.

There are two further specific contributions to knowledge. The first is that the outcomes of delirium, often thought of as universally bad, appear to have a bi-modal pattern. Half of the participants recovered well from delirium at three months, whereas the other half had significant adverse outcome. A second specific contribution to knowledge is that delirium occurred in 20% of patients with apparently normal or 'clean' brains based on cognitive testing. This group had no evidence of MCI or dementia and scored relatively well on detailed cognitive testing in the form of the ACEiii.

## 8.4 Recommendations for future research

### 8.4.1 Immune cell function

One of the proposed mechanisms of delirium discussed in chapter 1 is the link between systemic inflammation and central neuroinflammation, so called immune to brain communication. The function of specific immune cells in this link has not been investigated in delirium except in a paper demonstrating a link between natural killer cell activity and delirium (Hatta et al., 2014). In this pilot study, natural killer cell activity (NKCA), as swift responders to inflammation, predicted delirium in a post-operative population. Neutrophils, are vital components of the innate immune response known to undergo an age-related decline in function, and may therefore be a mediator of the link between systemic and central

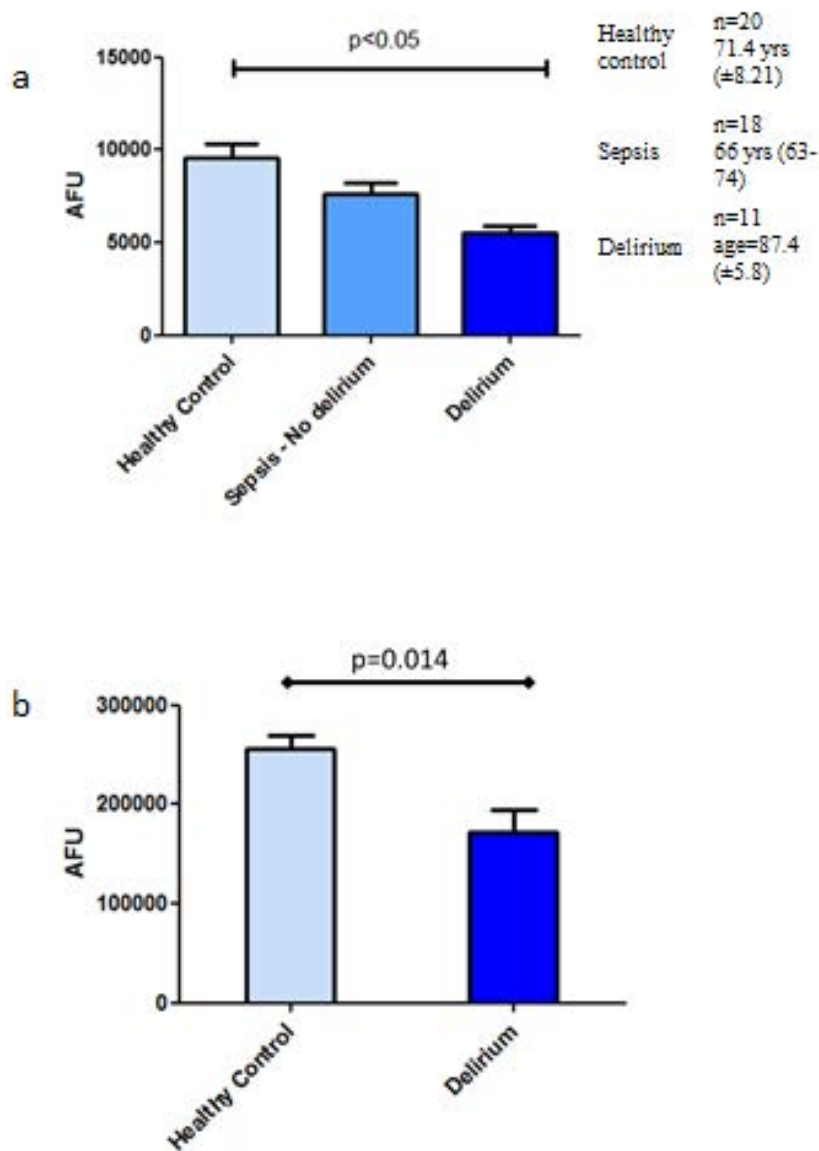


inflammation. Bactericidal neutrophil extracellular traps (NETs) are released from activated neutrophils and may also limit inflammation by degrading systemic pro-inflammatory cytokines. Also, neutrophil maturity and activation status may favour or inhibit NET release. Pilot work investigating this hypothesis will now be described.

Neutrophils were isolated from participants of the current cohort study (n=11), patients over 65 years old with sepsis, but without delirium (n=18) (both within 24 hours of admission), and healthy age matched controls (n=20). NET release was measured on isolated cells using fluorometry. Expression of surface markers CD16/CD11b/CD62L/CD63/CD66b was measured on neutrophils in whole blood by fluorescence-activated cell sorting.

NET release was decreased in neutrophils isolated from patients with delirium compared with septic patients without delirium and healthy controls (healthy elderly: 9538 arbitrary fluorescence units or AFU ( $\pm 804$ ), sepsis without delirium: 7606 AFU ( $\pm 619$ ) delirium patients: 5519 AFU ( $\pm 392$ ),  $p = <0.05$ ). CD16 expression, which is reduced in apoptotic cells that cannot form NETS, was decreased on neutrophils isolated from patients with delirium (Healthy elderly: 255795 AFU ( $\pm 13343$ ), delirium: 172026 AFU ( $\pm 23017$ ),  $p = 0.014$ ). There was no difference in CD11b/CD62L/CD63/CD66b. Figure 8-1 illustrates this.

This pilot work demonstrates that delirium was associated with decreased NET release and impaired neutrophil function. This may contribute to increasing systemic inflammation and lower bactericidal function. Both functions could contribute to the pathology of and adverse outcomes in delirium.



**Figure 8-1: a) Neutrophil extracellular trap formation (in arbitrary fluorescence units) is reduced in delirium, compared to those without, 2) Neutrophil CD16 expression (in arbitrary fluorescence units) is reduced in delirium compared to healthy controls**

Further research into the role of immune cell function and delirium would help to further characterise the neuroinflammatory response. Neutrophil function also includes the ability to migrate to sites of inflammation (so called chemotaxis and chemokinesis). Chemotaxis, the ability to migrate directly to sites, is decreased with age, however the impaired chemotaxis can be ameliorated by the inhibition of phosphoinositide 3-kinase (Sapey et al., 2014). Pharmacological phosphoinositide 3-kinase inhibitors include statin drugs, which have been shown observationally to be associated with reduced delirium in ITU settings (Page et al., 2014). A randomised controlled trial of simvastatin to prevent delirium in ITU patients is underway (Casarin et al., 2015).

Future research in immune cell function in delirium should also focus on the potentiation of the peripheral inflammatory response and how it interacts with neuroinflammation. This must examine both the acute response to inflammation, but also to resolution of that inflammation and how that impacts on longer term cognitive outcomes and dementia. Delirium may be a potential beneficial behavioural response to acute illness, allowing attention to be drawn to a person who is unwell and therefore gaining appropriate help. Hypoactive delirium is less likely to attract attention, so this may be an aberrant response and hence the subsequent associated adverse outcomes. It is plausible that the group with adverse outcomes following delirium have failure to resolve a beneficial inflammatory response, thus leading to an ongoing and negative inflammatory response.

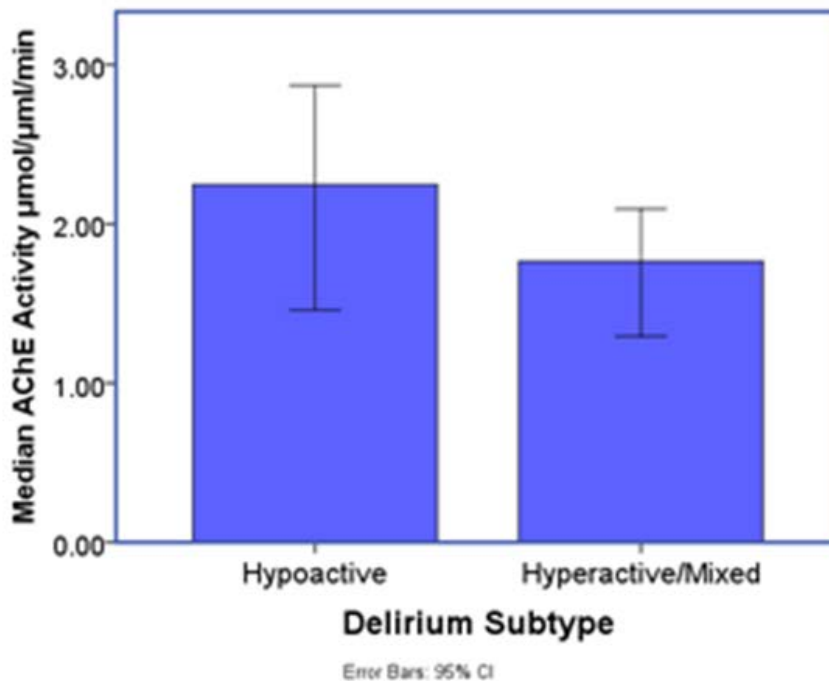
### 8.4.2 Differences in motor subtype

Further research should investigate pathophysiological differences between different motor subtypes. This is required to explain the biological plausibility of adverse outcomes seen with hypoactive delirium. Pilot work investigating this will now be described.

The cholinergic deficiency has been implicated in the pathophysiology of delirium (Hsieh et al., 2008). The enzyme acetylcholinesterase (AChE) inactivates acetylcholine by hydrolysing it to form acetate and choline. Reduced serum AChE activity from peripheral blood has been associated previously with development of delirium in a medical (White et al., 2005) and surgical population (Cerejeira et al., 2011, Cerejeira et al., 2012). Reduced serum AChE activity is associated with higher inpatient mortality (White et al., 2005) and frailty (Williams et al., 1989).

Directly measured serum AChE activity and clinical features of delirium was investigated. 55 participants from the current study had serum AChE activity measured using a colorimetric assay. AChE activity was expressed as a change in absorbance measured over 5 minutes ( $\mu\text{mol/ml/min}$ ).

The median AChE activity for the whole sample was  $1.81 \mu\text{mol/ml/min}$  (IQR 1.55). The hypoactive subtype was commonest (34 patients, 62%) while 12 (22%) had the hyperactive subtype and 9 (16%) the mixed subtype. Higher AChE activity was associated with an increased likelihood of the hypoactive subtype of delirium (OR=1.77, CI 1.05-2.97,  $p=0.031$ ). Figure 8-2 illustrates this.



**Figure 8-2: Acetylcholinesterase activity is higher in hypoactive delirium compared to mixed or hyperactive delirium**

This pilot work shows that higher AChE activity was associated with the hypoactive subtype, so suggesting for the first time a different underlying pathophysiology between different motor subtypes. Cholinergic neuronal pathways in the basal and rostral forebrain are involved in conscious awareness, attention and working memory, cognitive domains that are predominantly affected in hypoactive delirium (Terry and Buccafusco, 2003). The lower AChE activity seen in delirium may be due to a downregulation of the enzyme as a consequence of these reduced cholinergic neuronal pathways. By downregulating the enzyme there is increased Ach across the synapse. The higher AChE activity seen in hypoactive delirium may well represent a failure to downregulate AChE, leading to a greater hypo-cholinergic state and hence the clinical signs seen in hypoactive delirium. Pharmacological manipulation of the cholinergic pathway with AChE inhibitors has shown mixed results. A

number of case reports and small studies (Oldenbeuving et al., 2008) have shown positive results in the treatment and prevention of delirium with AChE inhibitors. However, more recently randomised controlled trials have had negative results (Gamberini et al., 2009, Overshott et al., 2010) and a major study had to be prematurely halted due to raised mortality in intensive care patients treated with rivastigmine (van Eijk et al., 2010). None of the major studies conducted a subgroups analysis looking at the effects of treatment depending on subtype. This opens the question of whether those with the hypoactive subtype may have preferentially benefitted from AChE inhibitor treatment, given their higher baseline activity of AChE. Future research should aim to provide personalised treatment depending of motor subtype or underlying pathophysiology.

#### 8.4.3 Novel methods for the investigation of pathophysiology

Novel methods to investigate the pathophysiology of delirium are needed. Investigation of immune cell function in the context of neutrophil NET production has been discussed earlier. However the investigation of other age related changes in immunity may offer important insights in to the pathophysiology of delirium. For example, neutrophil phagocytic function and super-oxide production is decreased in older patients with hip fracture, and subsequently associated with infection in the post-operative period (Butcher et al., 2003). This age related decline in response to trauma decreases the immune response to infection in older people, and this may well also increase the vulnerability to delirium.

Metabolomics is a systems biology approach to enable the global measurement of untargeted metabolites (Dunn, 2011). These metabolites can then be profiled into a metabolome and used to predict metabolic changes in delirium. This study of the global metabolic response to

delirium would allow for hypothesis generation of particular pathological pathways involved in both the development of delirium, but also in varied subtypes and outcomes.

Functional neuroimaging can allow for investigation real time changes in brain function. Although there is little work to date on functional neuroimaging in delirium (Choi et al., 2012, Soiza et al., 2008). There are practical issues with attempting neuroimaging during an episode of delirium, but a feasibility study has shown that functional MRI at discharge from ICU is possible (Jackson et al., 2015)

## 8.5 Two proposed programmes of research

From the thesis findings two research questions arise which should provide a basis for the further advancement of knowledge in the field. Firstly, the question of the benefit of diagnosis of dementia in hospital is a priority. The key question should be; does active diagnosis of dementia in general hospitals improve outcome? Through a prospective cohort of newly admitted older people, participants could be randomised to receive usual care (which currently includes mandated screening on admission) or an intervention. The intervention would consist of active case finding of MCI and dementia using performance based instruments, informant tools, and clinical assessment. The primary outcome measured should be the combined adverse outcome of new institutionalisation or death at 3 months. Secondary outcomes measured should be patient and carer satisfaction, incident delirium, length of hospital stay, and interventions for dementia such as cholinesterase prescription.

Secondly, the cognitive and functional trajectories of older people admitted to hospital and the link between these trajectories, and immunosenescence, need to be investigated as a priority. The key research question should be; what role does immunosenescence play in the cognitive

and functional trajectories of older people admitted to hospital? We know hospital admission in older people can have a major impact on functioning both physically and cognitively. This may be due to: the acute illness that led to hospital admission (such as delirium or infection), the illness itself is as a marker of a chronic disease (such as dementia), or indeed the effects of being hospitalised. Therefore the true outcomes of older people admitted to hospital in the context of cognitive disorders needs to be examined over a longer period of follow-up. By recruiting a cohort of older people who have been admitted to hospital for the first time, it would be possible to monitor these varied trajectories and outcomes. In hospital, diagnoses recorded should be of incident delirium, and dementia. Participants would then fall into 4 groups; delirium and dementia, delirium alone, dementia alone, and neither delirium nor dementia. Follow up would continue to monitor cognitive status, noting persistent delirium, new incident dementia or MCI, and worsening dementia. Measurement of immunosenescence and inflammation at ongoing time points would explore the biological mechanisms underpinning these trajectories, especially exploring persistence or resolution of the inflammatory response. Models of frailty and neurodegeneration in rodents could be used to explore the effects of acute inflammation on function and mortality. These would provide a platform for translation work. This greater understanding may lead to potential interventions to both ameliorate and ideally prevent the poor outcomes associated with hospital admission. This would have a major impact on the health of older people.



## 8.6 Future directions

### 8.6.1 Dementia and delirium 10 years in the future

Standardised rodent models of delirium will have allowed for the better understanding of the complex pathophysiology of delirium and dementia. Importantly these will have helped untangle the neuropathological links between dementia and delirium, with models of both existing neuropathology and ‘clean’ brains. Translational human studies of immune cell function, neuroinflammation, metabolomics, and the neuroendocrine systems will have confirmed these models in humans. New treatments developed from these rodent and human models will target immune modulation, manipulation of the neuro-endocrine system, and resolve acute neuroinflammation to arrest the chronic neurodegeneration after an episode of delirium. Delirium will be classified into different subgroups, and may even be seen as separate conditions. These subgroups will be along the lines of motor subtype (hypoactive or hyperactive), different precipitants (community acquired, sepsis driven, peri-operative) or in the context of dementia (DSD or delirium with no cognitive impairment).

In hospitals, risk scoring will enable identification of those needing more intensive treatment or different follow-up strategies. Delirium treatments may well be tailored to the subgroups discussed above. Evidence based timely diagnosis of dementia will take place on admission to hospital using well validated instruments with good discriminatory power. On recognition of dementia, structured non-pharmacological interventions will lead to improved outcomes, both short and long term. These interventions will include delirium prevention interventions as both delirium and dementia in general hospitals will be co-managed. A major intervention in dementia prevention and disease modification will be delirium prevention and treatment. Delirium prevention and treatment will be seen as preventative for developing dementia.

## 8.7 Conclusions

Both delirium and dementia are highly prevalent conditions in general hospitals and have a major impact on older people's health outcomes. Despite this the two conditions are relatively under-researched. Patients with delirium have a high degree of combined cognitive impairment (dementia or MCI) and a large proportion of this is undiagnosed. Therefore hospital admission allows an opportunity to improve recognition of these conditions. Delirium confers poor health outcomes on older people with it, but only half of older people with delirium suffer adverse outcomes. Predictors of these adverse outcomes are easily measured and provide some insights into the underlying pathophysiology of delirium, which is complex. Delirium and dementia in the general hospital are intricately linked and cannot be managed or researched in a mutually exclusive fashion. There are now broad opportunities to improve both the understanding of the link between these conditions at cellular and physiological level, but also to improve the care and follow-up of this very vulnerable group of patients.

## 9 Appendices

### 9.1 Appendix 1

The IQCODE and AD8 follow as given to the informants to complete.

Highlighted text is that altered from the original version

These versions are freely available at:

[http://www.bgs.org.uk/Publications/deliriumtk/contents/pdfs\\_word\\_files/iqcode.doc](http://www.bgs.org.uk/Publications/deliriumtk/contents/pdfs_word_files/iqcode.doc)

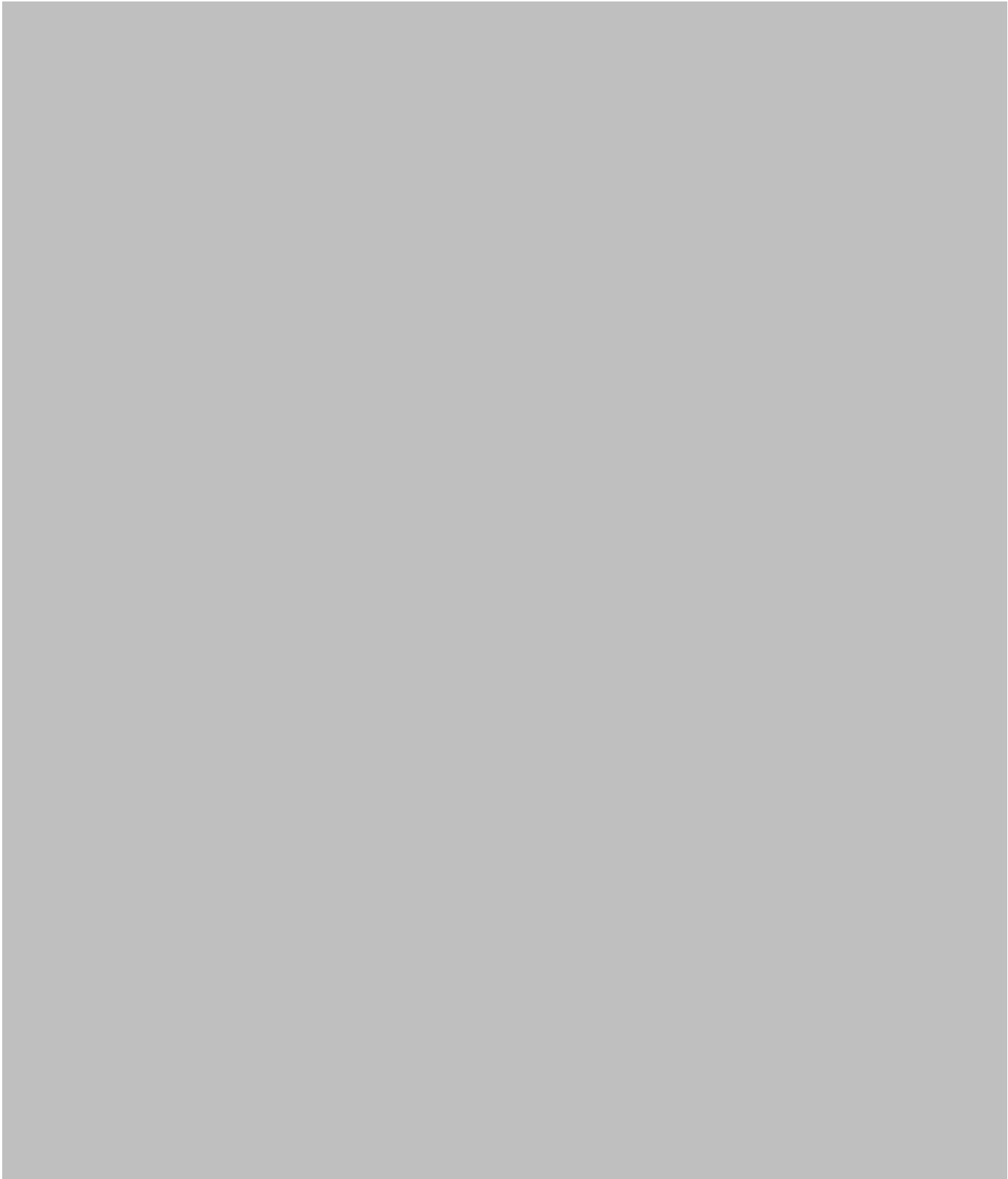
[http://knightadrc.wustl.edu/About\\_Us/PDFs/AD8form2005.pdf](http://knightadrc.wustl.edu/About_Us/PDFs/AD8form2005.pdf)

Study ID

DelHosp Study: Informant tools

Date:

RRK4658



Study ID

DelHosp Study: Informant tools

Date:

RRK4658



Study ID

DelHosp Study: Informant tools

Date:

RRK4658

**AD8 Dementia Screening Interview**

Patient ID# \_\_\_\_\_

CS ID# \_\_\_\_\_

Date: \_\_\_\_\_

Remember, "Yes, a change" indicates that there has been a change in the last several years caused by cognitive (thinking and memory) problems.	<b>YES, A change</b>	<b>NO, No change</b>	<b>N/A, Don't know</b>
<b>1.</b> Problems with judgment (e.g., problems making decisions, bad financial decisions, problems with thinking)			
<b>2.</b> Less interest in hobbies/activities			
<b>3.</b> Repeats the same things over and over (questions, stories, or statements)			
<b>4.</b> Trouble learning how to use a tool, appliance, or gadget (e.g., VCR, computer, microwave, remote control)			
<b>5.</b> Forgets correct month or year			
<b>6.</b> Trouble handling complicated financial affairs (e.g., balancing checkbook, income taxes, paying bills)			
<b>7.</b> Trouble remembering appointments			
<b>8. Daily</b> problems with thinking and/or memory			
<b>TOTAL AD8 SCORE</b>			

Adapted from Galvin JE et al, The AD8, a brief informant interview to detect dementia, *Neurology* 2005;65:559-564

Copyright 2005. The AD8 is a copyrighted instrument of the Alzheimer's Disease Research Center, Washington University, St. Louis, Missouri.

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## 9.2 Appendix 2

Search strategy for chapter 4 using MEDLINE

1. exp Dementia/
2. Cognition Disorders/
3. cognitive impairment.mp.
4. Hospitalization/
5. Inpatients/
6. exp Hospitals, General/
7. Diagnosis/
8. test\*.mp.
9. "Sensitivity and Specificity"/
10. "Predictive Value of Tests"/
11. 1 or 2 or 3
12. 4 or 5 or 6
13. 7 or 8 or 9 or 10
14. 11 and 12 and 13

15. 14

16. limit 15 to english language

For the second search involving specific tests the following terms were then searched for with search 12 above

‘6-CUT’ AND ‘six item cognitive screen’

AMT AND AMTS AND ‘Abbreviated mental test score’

MOCA AND ‘Montreal cognitive assessment’

ACE-R AND ‘Addenbrooke’s cognitive examination’

‘IQCODE’ AND ‘Informant questionnaire of cognitive decline in the elderly’

‘AD-8’

‘Sweet 16’



































































‘GPCOG’



## Appendix 2

Supplementary Table 1:

Results of the study quality assessment and assessment of risk bias by QUADAS -2

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
(O'Keeffe et al., 2011)							
(Leung et al., 2011)							
(Antonelli Incalzi et al., 2003)							
(Inouye et al., 1998)							
(Harwood et al., 1997)							
(Jitapunkul et al., 1991)							
(Erkinjuntti et al., 1987)							
(Klein et al., 1985)							
(Anthony et al., 1982)							
	 Low Risk	 High Risk	 Unclear Risk				

## 9.3 Appendix 3

Full search strategy for Medline for chapter 6

1. Follow-Up Studies/
2. Survival Analysis/
3. Survival Rate/
4. Prognosis/
5. Mortality/
6. predictor.mp.
7. "Outcome Assessment (Health Care)"/
8. exp Delirium/
9. 1 or 2 or 3 or 4 or 5 or 6 or 7
10. 8 and 9
11. limit 10 to (english language and humans)

Chapter 6, Supplementary Table 2 – Details of selected studies

Study, patient group and location	Study design and sample size (number with delirium)	Mean age (% female)	Delirium diagnosis	Outcome measured	Predictors identified	Statistical result presented (95% Confidence interval)
Adamis 2006 Acute admissions to inpatient geriatric ward ≥70 years UK	Observational prospective cohort 94 (33)	82.8 (59.6%)	CAM	LOS	Recovery from delirium <u>not</u> associated with LOS	No significant predictor identified
Bellelli 2014 Hip # patients Italy	Observational prospective cohort 199 (57)	84.3 (82.4%)	CAM and DSM-IV-R	6 month mortality	1.Duration of delirium (days) 2.Age (years) 3.ASA score 4.albumin All associated with 6 month mortality	1. HR 1.17 (1.07-1.28 p<0.05) 2. HR 1.07 (1.01-1.13 p<0.05) 3. HR 0.14 (0.04-0.49 p<0.05) 4. HR 0.42 (0.18-0.95 p<0.05)
Bellelli 2007 Inpatient geriatric ward ≥65 years Italy	Observational prospective cohort 188 (94)	79.6 (78%)	CAM	12 month mortality	Delirium superimposed on dementia associated with sores prognosis	HR 2.3 ( 1.1-5.5 p=0.04) compared to HR 1.6 ( 1.3-6.9 p=0.48) for delirium alone
Dasgupta 2013 General medical inpatients ≥70 years Canada	Observational prospective cohort 1235 (355)	82.6 (57.1%)	CAM	3 month “poor recovery” defined by death, institutionalisation or functional decline	1.Age 2.Higher ADL ability 3.Delirium severity 4.Hypoxia 5.ARF All associated with poor recovery	1.OR 1.14 (1.01-1.20 p<0.05) 2.OR 0.88 (0.78-0.99 p<0.05) 3.OR 1.16 (1.06-1.26 p<0.05) 4.OR 2.28 (1.12-4.64 p<0.05) 5.OR 2.69 (1.10-6.58 p<0.05)

Study, patient group and location	Study design and sample size (number with delirium)	Mean age (% female)	Delirium diagnosis	Outcome measured	Predictors identified	Statistical result presented (95% Confidence interval)
DeCrane 2011 Long term care facility USA	Observational prospective cohort 320 (90)	88.5 (77.8%)	CAM	12 month mortality	Delirium subtype <u>not</u> associated with 12 month mortality	No significant predictor identified
Eeles 2012 Acute medical admissions $\geq 75$ years UK	Observational prospective cohort 273 (102)	82.3 (55%)	DSM-IV	Survival over 5 years	Increasing frailty (by FI – frail = $>0.25$ ) associated with reduced survival	Difference in median survival time fo those with delirium: Not frail 359 days v frail 88 days (p=0.02)
Givens 2008 Hip # patients $\geq 65$ USA	Observational prospective cohort 126 (52)	79 (78.6%)	CAM	1 month new institutionalisation or death	Co-morbidity with depression AND/OR dementia associated with new institutionalisation or death at 1 month	All 3 adj OR 3.90 p=0.001), single comorbidity 1.78 (p=0.02), two comorbidities 1.83 (p=0.02) No 95% CI's given
Givens 2009 General medical inpatients $\geq 70$ USA	2 <sup>nd</sup> analysis of prospective cohort from trial 459 (62)	80 (60.3%)	CAM	1. New NH at 1 year 2. New NH or death at 1 year	Co-morbidity with depression increased risk of both outcomes	1.adj OR 5.06 (1.63-15.73 p<0.05) 2.adj OR 5.38 (1.57-18.38 p<0.05)
Gonzalez 2009 General medical inpatients $\geq 65$ Chile	Observational prospective cohort 542 (192)	78 (61.6%)	CAM	3 month mortality	Increased duration of delirium associated with increased mortality at 3 months	Duration > 48 hours associated with Adj HR 1.116 for mortality at 3 months (p<0.05)
Kakuma 2003 ED attendees $>65$ Canada	Observational prospective cohort 1268 (107)	80.1 (62.6%)	CAM	6 month mortality	Undetected delirium in ED associated with increased mortality at 6 months	HR 8.22 (1.69-39.89 p<0.05) compared with detected delirium

Study, patient group and location	Study design and sample size (number with delirium)	Mean age (% female)	Delirium diagnosis	Outcome measured	Predictors identified	Statistical result presented (95% Confidence interval)
Keily 2007 Post-acute care USA	Observational prospective cohort 457 (457)	84 (64.5%)	CAM	12 month mortality	Hypoactive delirium (according to MDAS) associated with increased mortality at 1 year	HR 1.62 (1.11-2.37 p<0.05) compared to 'normal' psychomotor delirium subtype
Keily 2009 Post-acute care USA	Observational prospective cohort 412 (412)	84 (64.8%)	CAM	12 month mortality	Persistence of delirium at 6 months associated with increased 1 year mortality	Adjusted HR 2.9 (1.9-4.4 p<0.05) compared to resolved delirium
Kelly 2001 Inpatient geriatric ward USA	Observational prospective cohort 214 (61)	89 (72%)	CAM	Discharge and 3 month mortality	1.MDAS >24 associated with higher mortality by discharge and at 3 months 2.No improvement in MDAS associated with in hospital mortality 3.No association with motor subtype (MDAS) and mortality	Compared proportions by Chi-Squared p values all <0.05
Kaponen 1994 EAPCN 1 General medical inpatients Finland	Selected subjects from prospective cohort 69 (69)	75 (58%)	DSM – III	Survival over 4 years	Initial CSF AChE activity associated with life span after delirium	Z=2.30, p=0.018 according to proportional hazards model
Kaponen 1994 EAPCN 2 General medical inpatients Finland	Selected subjects from prospective cohort 69 (69)	75 (58%)	DSM – III	1. Survival over 4 years 2. Prolonged institutional care	1.CSF 5-HIAA associated with decreased survival at 4 years, 2. reduced CSF 5-HIAA associated with prolonged institutional care	1. Z=2.93 p=0.007 according to proportional hazards model 2. lower levels, p=0.01

Study, patient group and location	Study design and sample size (number with delirium)	Mean age (% female)	Delirium diagnosis	Outcome measured	Predictors identified	Statistical result presented (95% Confidence interval)
Lee 2011 Hip # patients South Korea	Observational prospective cohort 232 (70)	79 (74.6%)	CAM and psychiatry interview	24 month mortality	Delirium > 4 weeks not associated with worse mortality then in those with delirium < 4 weeks	Survival rate 63.6% in prolonged delirium compared to 73.5% in short, p>0.05
Leonard 2008 Palliative care unit Ireland	Observational prospective cohort 121 (121)	70.2 (50%)	CAM and DSM-IV	Survival time in days	Cognitive test for delirium score, age, presence of organ failure associated with reduced survival time in days	Linear regression performed (all p values <0.05)
Marcantonio 2000 Hip # patients USA	Observational prospective cohort 126 (52)	79 (79%)	CAM	1 month death or institutionalisation	Persistent delirium significantly associated with death or institutionalisation	Difference in proportion of outcome Chi Squared p<0.05
Marcantonio 2002 Hip # patients USA	Observational prospective cohort 122 (49)	79 (79%)	CAM	6 month death or institutionalisation	1.Delirium severity by MDAS score > 12.44 associated with death or institutionalisation. 2.Hyperactive delirium associated with increased death or institutionalisation at 1 month	1.RR 3.1 (1.2-8.2 p<0.01) 2.OR 6.0 (1.3-29.0 p<0.01)
McAvay 2006 General medical inpatients ≥ 70 years USA	2nd analysis of prospective cohort from trial 433 (55)	79.8 (60.3%)	CAM	12 month death or institutionalisation	Delirium at discharge associated with institutionalisation or death at 12 months compared to delirium resolved at d/c	Chi Square test p=0.03 Adj HR 1.73 (0.92–3.26)
McCusker 2002 General medical inpatients ≥ 65 years Canada	Observational prospective cohort 243 (243)	Mean age not specified (60.5%)	CAM	12 month mortality	1.Dementia and delirium associated with increased 12 month mortality compared to neither 2.Delirium alone without dementia associated with increased 12 month mortality (dementia protective)	1.HR 1.96 (0.76-5.05) 2. HR 3.77 (1.39-10.20)

Study, patient group and location	Study design and sample size (number with delirium)	Mean age (% female)	Delirium diagnosis	Outcome measured	Predictors identified	Statistical result presented (95% Confidence interval)
Meagher 2011 Palliative care unit patients Ireland	Observational prospective cohort 100 (100)	70.2 (49%)	DSM IV	Mortality at 30 days after entry	Hypoactive delirium (according to DMSS) associated with increased mortality at 30 days compared with other motor subtypes	Difference between mortality rate by Chi squared (p=0.03)
Morandi 2014 Hospital rehabilitation unit ≥65 years Italy	Observational prospective cohort 2642 (323)	77 (73%)	DSM-IV-TR	1.12 month institutionalisation 2.12 month mortality	1. Delirium superimposed on dementia associated with higher 12 month institutionalisation 2. Delirium superimposed on dementia associated with higher 12 month mortality	1.OR=5 (2.8-8.9 p<0.01) for DSD compared to OR=2.41(1.02-5.66 p<0.01) for delirium alone p<0.01 2.OR=1.76 (1.10-2.86, p<0.01) for DSD compared to OR=1.54 (0.77-3.07) for delirium alone
Slor 2013 Hip # patients Netherlands	Selected from observational prospective cohort 169 (62 but 30 included in analysis)	85.1 (77%)	CAM	LOS or inpatient mortality	Delirium subtype <u>not</u> associated with LOS or inpatient mortality	No significant predictor identified
Sylvestre 2006 General medical inpatients >65 years Canada	Observational prospective cohort 230 (230)	84 (54.3%)	CAM	Time to death over 12 months	Delirium phenomenology divided into 5 clusters <u>not</u> significantly associated with survival	No significant predictor identified
Tsai 2012 General medical inpatients ≥ 65 years Taiwan	Observational prospective cohort 614 (172)	74.7 (47.9%)	DSM-IV-TR	12 month mortality	Age >85 years and LOS both associated with increased mortality at 1 year	Age >85 HR 2.77 (1.31-5.85 p=0.007) compared to < 70 yrs LOS HR 1.013 (1.002-1.019 p<0.001)

Study, patient group and location	Study design and sample size (number with delirium)	Mean age (% female)	Delirium diagnosis	Outcome measured	Predictors identified	Statistical result presented (95% Confidence interval)
Yang 2009 Post-acute care $\geq$ 65 years USA	Observational prospective cohort 441(441)	84.1 (64.6%)	CAM	6 month mortality	Hypoactive delirium and dementia associated with increased mortality at 6 months	Hypoactive subtype– HR 3.98 (1.76-8.98) compared to normal motor subtype

Abbreviations used: ADL = activities of daily living, adj = adjusted , ASA = American Society of Anaesthetists score, CAM = Confusion Assessment Method, CSF AChE = cerebrospinal fluid acetylcholinesterase activity, CSF-5-HIAA = cerebrospinal fluid 5-Hydroxyindoleacetic acid, DSD = delirium superimposed on dementia, DSM = Diagnostic and Statistical Manual of Mental Disorders, FI = Rockwood Frailty Index, Hip # = fractured neck of femur, HR = hazard ratio, LOS = length of stay in hospital days, MDAS = Memorial delirium assessment scale, NH = nursing home, OR = odds ratio.

95% confidence intervals in brackets after all HR and OR given



Appendix 3, supplementary table 3: Newcastle-Ottawa scores for selected studies in chapter

6

Study	Selection (max 4)	Comparability (max 2)	Exposure (max 3)
Adamis 2006	****	**	***
Bellelli 2014	****	**	**
Bellelli 2007	****	**	***
Dasgupta 2013	***	**	**
DeCrane 2011	****	-	***
Eeles 2012	****	-	**
Givens 2008	****	**	***
Givens 2009	****	**	***
Gonzalez 2009	****	**	***
Kakuma 2003	****	**	***
Keily 2007	****	**	***
Keily 2009	****	**	***
Kelly 2001	****	-	***

Study	Selection (max 4)	Comparability (max 2)	Exposure (max 3)
Kaponen 1994	****	-	***
Kaponen 1994	****	-	***
Lee 2011	****	-	***
Leonard 2008	***	-	***
Marcantonio 2000	****	**	**
Marcantonio 2002	***	**	**
McAvay 2006	****	-	***
McCusker 2002	****	**	***
Meagher 2011	****	**	***
Morandi 2014	***	**	**
Slor 2013	****	-	***
Sylvestre 2006	****	**	**
Tsai 2012	****	-	***
Yang 2009	****	**	**

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